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Drug-Induced QT Prolongation and Torsades de Pointes: An All-Exclusive Relationship or Time for an Amicable Separation?

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ABSTRACT

QT prolongation was perceived as a major antiarrhythmic mechanism, but soon became a surrogate for torsades de pointes (TdP) instead. Drugs that prolong the QT interval range from having potent torsadogenic activity to no proarrhythmic action and even antiarrhythmic effects. Blockade of hERG channels is the primary cause of TdP, but blockade/activation of other channels can also be torsadogenic. TdP is primarily caused by disturbances of TRIaD, but disturbance of wavelength can also contribute to TdP (where TRIaD is triangulation, reverse use dependence, instability and dispersion, and wavelength equals conduction velocity times effective refractory period). The above proarrhythmic parameters do not only result in TdP, but can also lead to ventricular tachycardia (VT) and ventricular fibrillation (VF). Note that QT prolongation (not listed as a causal factor) yields many false positives (potentially depriving patients from much needed drugs) and false negatives (potentially exposing patients to lethal arrhythmias). Thus, drug-induced QT prolongation is a bad surrogate for TdP, VT or VF; it is high time to move away from an oversimplified and erroneous surrogate.

Dopamine Agonists and Impulse Control Disorders: A Complex Association

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ABSTRACT

Impulse control disorders (ICDs) are a well-known adverse effect of dopamine agonists (DAAs). This critical review aims to summarize data on the prevalence and factors associated with the development of an ICD simultaneous to DAA use. A search of two electronic databases was completed from inception to July 2017. The search terms were medical subject headings (MeSH) terms including “dopamine agonists” AND “disruptive disorders”, “impulse control disorders”, or “conduct disorders”. Articles had to fulfill the following criteria to be included: (i) the target problem was an ICD; (ii) the medication was a dopaminergic drug; and (iii) the article was an original article. Of the potential 584 articles, 90 met the criteria for inclusion. DAAs were used in Parkinson’s disease (PD), restless legs syndrome (RLS) or prolactinoma. The prevalence of ICDs ranged from 2.6 to 34.8% in PD patients, reaching higher rates in specific PD populations; a lower prevalence was found in RLS patients. We found only two studies about prolactinoma. The most robust findings relative to the factors associated with the development of an ICD included the type of DAA, the dosage, male gender, a younger age, a history of psychiatric symptoms, an earlier onset of disease, a longer disease duration, and motor complications in PD. This review suggests that DAA use is associated with an increased risk in the occurrence of an ICD, under the combined influence of various factors. Guidelines to help prevent and to treat ICDs when required do exist, although further studies are required to better identify patients with a predisposition.

Cardiac Harms of Sofosbuvir: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Sofosbuvir is a new direct-acting pyrimidine nucleotide analogue antiviral drug that has shown remarkable efficacy in the treatment of hepatitis C in clinical trials. However, observational anecdotal data have recently suggested an increased risk of serious bradycardia among patients treated with sofosbuvir and amiodarone.

Objective: We aimed to estimate and characterize the cardiac safety of sofosbuvir by performing a systematic review of randomized controlled trials (RCTs).

Methods: We conducted a systematic review of RCTs (PROSPERO 2016: CRD42016033109) comparing sofosbuvir and non-sofosbuvir regimens in patients with chronic hepatitis C by searching the MEDLINE, Embase, and Cochrane Library databases up to January 2017. Non-published data were obtained from the sofosbuvir marketing authorization holder. Random-effects meta-analysis was performed to derive pooled estimates of relative risks (RRs) and corresponding 95% confidence intervals (CIs).

Results: Six trials, enrolling 2346 patients (1625 treated with sofosbuvir), were included. The overall risk of bias across studies was moderate. The risk of reported cardiac events (RR 0.87; 95% CI 0.41–1.85), arrhythmias (RR 0.93; 95% CI 0.34–2.51), bradycardia (RR 0.47; 95% CI 0.04–5.20), and tachycardia (RR 0.91; 95% CI 0.20–4.20) were not significantly different between sofosbuvir and non-sofosbuvir regimens. The risks of reported syncope, presyncope, loss of consciousness, or palpitations were similar among those receiving sofosbuvir regimens and controls.

Conclusions: The pooled data from RCTs did not show an increased risk of cardiac outcomes, including arrhythmias (and bradycardia), among sofosbuvir-treated patients, although the overall quality of the evidence supporting this conclusion was very low.

Enrollment and Retention in 34 United States Pregnancy Registries contrasted with the Manufacturer's Capture of Spontaneous Reports for Exposed Pregnancies

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ABSTRACT

Introduction: Pregnancy registries and spontaneous reports are essential pharmacovigilance tools to evaluate drug safety during pregnancy.

Objectives: The aim of this study was to evaluate postmarket capture of exposed pregnancies.

Methods: Pregnancy registries for drugs and biologics were identified in a systematic review. Through a standardized questionnaire, manufacturers provided information on (1) pregnancy registry enrollment and retention, and (2) worldwide receipt of spontaneous reports for exposed pregnancies. A validated algorithm for live-birth pregnancies allowed calculation of exposure rates per 100,000 live births using claims data.

Results: Among 34 products with a pregnancy registry, median (interquartile range) registry enrollment was 36 pregnancies (5–258) and median spontaneous report capture was 450 pregnancies (89–1192). Products used in >20/100,000 live births had a median registry enrollment of 490 pregnancies and median capture of 1061 spontaneously reported exposed pregnancies. Lower median registry enrollment and spontaneous report capture was observed for products used in 0.5–20/100,000 live births (36 from registries, 541 spontaneous reports) and <0.5/100,000 live births (3 from registries, 41 spontaneous reports). Among 24 registries enrolling ≥10 pregnancies, median capture of pregnancy outcomes (e.g. live birth, spontaneous abortion) was 83.9%. For 19 registries enrolling ≥10 infants, the median proportion of infants achieving protocol-specified follow-up was 89.9% for up to 4 weeks post-birth, 75.0% for 1–5 months, and 57.1% for ≥6 months.

Conclusions: Relatively higher product utilization among pregnant women predicted greater pregnancy registry enrollment. For products rarely used during pregnancy, registry enrollment was low and differences in registry enrollment compared with worldwide spontaneous report receipt were most pronounced. Products with very low utilization levels during pregnancy may require a combination of worldwide pharmacovigilance, pregnancy registries, and additional study methods to achieve adequate surveillance.

Antidepressant-Induced Acute Liver Injury: A Case–Control Study in an Italian Inpatient Population

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ABSTRACT

Introduction: Pre-marketing clinical trials show that antidepressant-induced liver injury seems to be a rare adverse event. Because of short follow-up trial duration, the incidence of liver injury due to antidepressant use could be underestimated.

Objectives: We aimed to quantify the risk of acute liver injury associated with antidepressant use through a case–control analysis among an inpatient population.

Methods: A multicenter study was carried out in nine Italian hospitals from October 2010 to January 2014, within the DILI-IT (Drug-Induced Liver Injury in Italy) study project. After exclusion of all patients with a clear competing cause of liver injury, cases were defined as adults admitted to the hospital with a diagnosis of acute liver injury, while controls had any other acute clinical condition not related to the liver. Antidepressant exposure was evaluated within 90 days prior to the date of the first sign/symptom of liver injury. Odds ratio (OR) with 95% confidence interval (95% CI) was calculated as a measure of risk estimates for liver injury.

Results: We included 17 cases exposed to antidepressants matched to 99 controls. According to the features of liver injury, all cases showed symptomatic liver function test abnormalities at hospital admission, with the main signs/symptoms represented by fatigue, nausea, asthenia, or dark urine. Citalopram was the antidepressant mostly involved in the increase of liver enzymes, mainly alanine aminotransferase. Compared with non-use, current use of antidepressants was associated with a significantly increased risk of liver injury (adjusted OR, ORADJ, 1.84; 95% CI 1.02–3.32). Specifically, an increased, but not significant, risk of developing liver injury was observed for citalopram, a selective serotonin-reuptake inhibitor (ORADJ 1.82; 95% CI 0.60–5.53).

Conclusion: The use of antidepressants is not as safe in terms of liver injury as expected; instead, the risk of antidepressant-induced liver injury is likely underestimated. The lack of significance does not reflect the absence of risk, but rather suggests the need to evaluate it in a wider setting of antidepressant users.

Deaths from Medicines: A Systematic Analysis of Coroners' Reports to Prevent Future Deaths

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ABSTRACT

Introduction: Since legislation in 2009, coroners in England and Wales must make reports in cases where they believe it is possible to prevent future deaths. We categorised the reports and examined whether they could reveal preventable medication errors or novel adverse drug reactions.

Methods: We examined 500 coroners' reports by pre-defined criteria to identify those in which medicines played a part, and to collect information on coroners' concerns.

Results: We identified 99 reports (100 deaths) in which medicines or a part of the medication process or both were mentioned. Reports mentioned anticoagulants (22 reports), opioids (17), antidepressants (17), drugs of abuse excluding opioids (12 deaths) and other drugs. The most important concerns related to adverse reactions to prescribed medicines (22), omission of necessary treatment (21), failure to monitor treatment (17) and poor systems (17). These were related to defects in education or training, lack of clear guidelines or protocols and failure to implement existing guidelines, among other reasons. Most reports went either to NHS Hospital Trusts or to local trusts. The responses of addressees were rarely published. We identified four safety warnings from the Medicines and Healthcare Products Regulatory Agency that were based on coroners' warnings.

Conclusion: Coroners' reports to prevent future deaths provide some information on medication errors and adverse reactions. They rarely identify new hazards. At present they are often addressed to local bodies, but this could mean that wider lessons are lost.

Treatment of Medication-Related Osteonecrosis of the Jaw and its Impact on a Patient's Quality of Life: A Single-Center, 10-Year Experience from Southern Italy

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ABSTRACT

Introduction: No official guidelines are available for the management of medication-related osteonecrosis of the jaw (MR-ONJ). The additional benefit of surgery after pharmacological treatment is debated by both clinicians and patients.

Objective: The aim of this study was to evaluate the changes in patients' MR-ONJ-related quality of life (QoL) after pharmacological treatment with or without surgery in a large cohort affected by MR-ONJ.

Methods: Anonymized data on patients diagnosed with MR-ONJ were extracted from the database of the Osteonecrosis of the Jaw Treatment Center (University of Messina, Italy) in the years 2005–2015. QoL was evaluated at the moment of MR-ONJ diagnoses (T0), after pharmacological treatment with or without surgery (T1 and T2, respectively), based on scores from the European Organisation for Research and Treatment of Cancer (EORTC) QOL Module for Head and Neck Cancer (global oral health status [GOHS]) and a visual analog scale (VAS), stratified by indication for use.

Results: Among 100 patients, 36% were affected by osteoporosis (OSTEO group) and 64% were affected by cancer (ONC group). Considering T0, QoL scores were higher in the OSTEO group then in the ONC group. At T1, GOHS and VAS increased in both groups (OSTEO group: +9.9% and +39.9%; ONC group: +35.4 and +97.2%, respectively). Pharmacological treatment was effective in reducing pain (OSTEO group: −22.0%; ONC group: −44.8%), and social contact troubles (OSTEO group: −40.3%; ONC group: −26.7%). At T2, GOHS and VAS further increased. Scores related to 'pain' and the troubles related to the 'social dimension' also decreased (OSTEO group: −91.3% and −72.0%; ONC group: 50.8% and −16.4%, respectively).

Conclusions: MR-ONJ-related QoL increased after pharmacological treatment and, more notably, after surgery, which may offer benefits to selected patients. QoL data may help clinicians in promoting tailored management of MR-ONJ.

Evaluation of Electronic Healthcare Databases for Post-Marketing Drug Safety Surveillance and Pharmacoepidemiology in China

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ABSTRACT

Introduction: Electronic healthcare databases (EHDs) are used increasingly for post-marketing drug safety surveillance and pharmacoepidemiology in Europe and North America. However, few studies have examined the potential of these data sources in China.

Methods: Three major types of EHDs in China (i.e., a regional community-based database, a national claims database, and an electronic medical records [EMR] database) were selected for evaluation. Forty core variables were derived based on the US Mini-Sentinel (MS) Common Data Model (CDM) as well as the data features in China that would be desirable to support drug safety surveillance. An email survey of these core variables and eight general questions as well as follow-up inquiries on additional variables was conducted. These 40 core variables across the three EHDs and all variables in each EHD along with those in the US MS CDM and Observational Medical Outcomes Partnership (OMOP) CDM were compared for availability and labeled based on specific standards.

Results: All of the EHDs' custodians confirmed their willingness to share their databases with academic institutions after appropriate approval was obtained. The regional community-based database contained 1.19 million people in 2015 with 85% of core variables. Resampled annually nationwide, the national claims database included 5.4 million people in 2014 with 55% of core variables, and the EMR database included 3 million inpatients from 60 hospitals in 2015 with 80% of core variables. Compared with MS CDM or OMOP CDM, the proportion of variables across the three EHDs available or able to be transformed/derived from the original sources are 24–83% or 45–73%, respectively.

Conclusions: These EHDs provide potential value to post-marketing drug safety surveillance and pharmacoepidemiology in China. Future research is warranted to assess the quality and completeness of these EHDs or additional data sources in China.

From Big Data to Smart Data for Pharmacovigilance: The Role of Healthcare Databases and Other Emerging Sources

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ABSTRACT

In the last decade 'big data' has become a buzzword used in several industrial sectors, including but not limited to telephony, finance and healthcare. Despite its popularity, it is not always clear what big data refers to exactly. Big data has become a very popular topic in healthcare, where the term primarily refers to the vast and growing volumes of computerized medical information available in the form of electronic health records, administrative or health claims data, disease and drug monitoring registries and so on. This kind of data is generally collected routinely during administrative processes and clinical practice by different healthcare professionals: from doctors recording their patients' medical history, drug prescriptions or medical claims to pharmacists registering dispensed prescriptions. For a long time, this data accumulated without its value being fully recognized and leveraged. Today big data has an important place in healthcare, including in pharmacovigilance. The expanding role of big data in pharmacovigilance includes signal detection, substantiation and validation of drug or vaccine safety signals, and increasingly new sources of information such as social media are also being considered. The aim of the present paper is to discuss the uses of big data for drug safety post-marketing assessment.

Overview of Pharmacovigilance System in Vietnam: Lessons Learned in a Resource-Restricted Country

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ABSTRACT

Drug safety issues in developing countries are complex and sensitive, and health authorities cannot always simply implement decisions from developed countries because the health system, disease patterns, and lists of marketed drugs all differ. A system for proactive and effective surveillance of drugs in each nation is needed to identify and manage the exact drug-related problems faced by patients in these countries. Vietnam launched its university-based National Drug Information and Adverse Drug Reaction Monitoring Centre (NDIADRMC) in 2009, a significant step towards catching up with international trends. Although the center is still in its infancy and has limited resources, it has attained some achievements and largely met the minimum World Health Organization requirements for a functional pharmacovigilance center. The number of reports has increased rapidly, with some important signals generated from the national database leading to regulatory actions at a national level. In addition, this system can help detect drug-quality problems that are less common in developed countries. The success of the quantity and quality of reporting, risk assessment, and communication is still limited compared with more developed systems. A number of opportunities remain to enhance the system, particularly in risk communication and evaluation of the impact of pharmacovigilance, and to apply reporting outcomes to reduce drug-related risks throughout the country. More internal and external support is needed to develop a stronger and more comprehensive pharmacovigilance system.

Use of Antihypertensive Drugs and Risk of Malignant Melanoma: A Meta-analysis of Observational Studies

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ABSTRACT

Introduction: Several antihypertensive drugs are photosensitizing and may promote the development of malignant melanoma (MM), but evidence remains inconsistent. We sought to quantify the association between use of antihypertensive drugs and MM risk.

Methods: We systematically searched PubMed, Embase, and CENTRAL from inception to August 17, 2017 to identify observational studies that reported the MM risk associated with the use of antihypertensive drugs. A random-effects meta-analysis was used to estimate the odds ratio (OR) with 95% confidence interval (CI).

Results: Overall, we included eight observational studies (two cohort studies and six case–control studies). Compared with non-use, use of diuretics (OR 1.10; 95% CI 1.03–1.17) or β-adrenergic blocking agents (OR 1.19; 95% CI 1.04–1.37) was significantly associated with increased risk of MM. The use of angiotensin-converting enzyme inhibitors (OR 1.08; 95% CI 0.95–1.23), angiotensin II receptor blockers (OR 1.12; 95% CI 0.95–1.31), and calcium channel blockers (OR 1.12; 95% CI 0.72–1.74) was not significantly associated with increased risk of MM.

Conclusions: Current evidence from observational studies suggests that use of diuretics or β-adrenergic blocking agents may be associated with increased risk of MM. Further large well-conducted prospective studies are required to confirm our findings.

Safety of Russian-Backbone Trivalent, Live Attenuated Seasonal Influenza Vaccine in Healthy Subjects: Open-Label, Non-randomized Phase 4 Study

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ABSTRACT

Introduction and Aim: A trivalent live attenuated influenza vaccine (Nasovac-S®) was developed and licensed in India. A phase 4 study was conducted to assess safety.

Methodology: This non-randomized, open-label, single-arm study among individuals ≥ 2 years of age involved administration of 0.5 mL of Nasovac-S intranasally, with a 1-month follow-up after vaccination. Adverse events (AEs) were collected via structured diaries.

Results: Among 500 vaccinated subjects, 160 were between 2 and 17 years of age, 240 were 18–49 years old and 100 were 50 years and older. A total of 533 solicited reactions were reported. The majority of these reactions were mild, and almost all of them resolved without any sequelae. A total of 20% of subjects reported at least one local solicited reaction, and 23% reported at least one systemic solicited reaction. None of the 45 unsolicited AEs reported by 37 subjects (7.4%) were causally related to the study vaccine.

Conclusions: The data from the study adds to the existing safety database of Nasovac-S.

Preferences of Patients and Pharmacists with Regard to the Management of Drug–Drug Interactions: A Choice-Based Conjoint Analysis

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ABSTRACT

Introduction: The management of drug–drug interactions (DDIs) is a complex process in which risk–benefit assessments should be combined with the patient's perspective.

Objective: The aim of this study was to determine patients' and pharmacists' preferences regarding DDI management.

Methods: We conducted a choice-based conjoint survey about a fictitious DDI concerning the combination of a cardiovascular drug and an antibiotic for pneumonia. Patients and pharmacists had to choose 12 times between two management options. The options were described by five attributes, including risk, benefit and practical consequences. Each attribute could have two different levels, which were varied over the choice tasks. Latent class analysis was used to identify potential classes of respondents with distinct patterns of similar preferences.

Results: In total, 298 patients and 178 pharmacists completed the questionnaire. The latent class model for both patients and pharmacists resulted in three classes. For patients, in one class the most importance was attached to avoiding switch of medication (class probability 20%), in a second class to fewer adverse events (41%), and in a third class to blood sampling (39%). For pharmacists, again one class attached the highest importance to avoiding switch of medication (31%). The other classes gave priority to curing pneumonia (31%) and avoiding blood sampling (38%).

Conclusion: The results showed diverging preferences regarding DDI management among both patients and pharmacists. Different groups attached different value to risk and benefit versus practical considerations. Awareness of existing variability in preferences among and between pharmacists and patients is a step towards shared decision making in DDI management.

Study Design and Evaluation of Risk Minimization Measures: A Review of Studies Submitted to the European Medicines Agency for Cardiovascular, Endocrinology, and Metabolic Drugs

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ABSTRACT

Introduction: Studies measuring the effectiveness of risk minimization measures (RMMs) submitted by pharmaceutical companies to the European Medicines Agency are part of the post-authorization regulatory requirements and represent an important source of data covering a range of medicinal products and safety-related issues. Their objectives, design, and the associated regulatory outcomes were reviewed, and conclusions were drawn that may support future progress in risk minimization evaluation.

Methods: Information was obtained from risk management plans, study protocols, clinical study reports, and assessment reports of 157 medicinal products authorized for cardiovascular, endocrinology, and metabolic indications. We selected observational studies measuring, as outcomes of interest, the relationship between the RMMs in place and (1) implementation measures, such as clinical knowledge or physicians` compliance to recommendations contained in the RMMs; and (2) occurrence or reduced severity of the adverse drug reactions for which the RMMs were required.

Results: Of 59 eligible studies (24 completed, 35 ongoing), 44 assessed implementation measures, whereas only 15 assessed safety outcomes (1 study as a single endpoint and 14 studies with other endpoints). Fifty-one studies used non-experimental designs and 25 studies employed electronic healthcare databases for analysis. Of the 24 completed studies, 17 were considered satisfactory and supported immediate regulatory decision making, 6 were considered inconclusive and required new evaluations, and 1 was terminated early because new safety restrictions were required, thereby necessitating a new evaluation. Compliance with agreed deadlines was considered acceptable in 21 of 24 completed studies; the average time for a submission was 37 months (standard deviation ± 17), with differences observed by type of data source employed.

Conclusions: Three important gaps in the evaluation plans of RMMs were identified: lack of early feedback on implementation, limited evaluation of safety outcomes, and inability to provide information on the effectiveness from an integrated measurement of different elements of a set of risk minimization tools. More robust evidence is needed to advance regulatory science and support more rapid adjustment of risk minimization strategies as needed.

Safety Concerns Reported by Patients Identified in a Collaborative Signal Detection Workshop using VigiBase: Results and Reflections from Lareb and Uppsala Monitoring Centre

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ABSTRACT

Introduction: Patient reporting in pharmacovigilance is important and contributes to signal detection. However, descriptions of methodologies for using patient reports in signal detection are scarce, and published experiences of how patient reports are used in pharmacovigilance are limited to a few individual countries.

Objective: Our objective was to explore the contribution of patient reports to global signal detection in VigiBase.

Methods: Data were retrieved from VigiBase in September 2016. Drug–event-combination series were restricted to those with >50% patient reports, defined as reporter type "Consumer/non-health professional" per E2B reporting standard. vigiRank was applied to patient reports to prioritize combinations for assessment. Product information for healthcare professionals (HCPs) as well as patient information leaflets (PILs) were used as reference for information on adverse drug reactions (ADRs). Staff from the Uppsala Monitoring Centre and the Netherlands Pharmacovigilance Centre Lareb categorized the combinations. Potential signals proceeded to a more in-depth clinical review to determine whether the safety concern should be communicated as a "signal."

Results: Of the 212 combinations assessed, 20 (9%) resulted in eight signals communicated within the World Health Organization (WHO) programme for international drug monitoring. Review of PILs revealed insufficient ADR descriptions for patients and examples of poor consistency with product information for HCPs. Patient narratives provided details regarding the experience and impact of ADRs and evidence that patients make causality and personal risk assessments.

Conclusions: Safety concerns described in patient reports can be identified in a global database including previously unknown ADRs as well as new aspects of known ADRs. Patient reports provide unique information valuable in signal assessment and should be included in signal detection. Novel approaches to highlighting patient reports in statistical signal detection can further improve the contribution of patient reports to pharmacovigilance.

All-Cause and Drug-Related Medical Events Associated with Overuse of Gabapentin and/or Opioid Medications: A Retrospective Cohort Analysis of a Commercially Insured US Population

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ABSTRACT

Introduction: Overuse of gabapentin and/or opioids occurs in a small percentage of patients at > 3-fold labeled dosages. Gabapentin may potentiate opioid effects.

Objective: The aim was to assess patient harm, defined as use of inpatient hospital (IPH) or emergency department (ED) services, associated with overuse of gabapentin with or without concomitant overuse of opioids.

Data source: Data were sourced from the Truven Health MarketScan® Commercial Claims and Encounters database, for the years 2013–2015.

Eligibility criteria: The eligibility criteria were two or more claims (billed encounters) and ≥120 days of treatment with gabapentin and/or opioids.

Methods: Cohort identification was based on daily-dosage thresholds of 50 morphine-milligram equivalents and 3600 mg of gabapentin in a 12-month follow-up: (1) no overuse; (2) mild overuse (two or more claims or two or fewer calendar quarters over threshold); and (3) sustained overuse (three or more over-threshold calendar quarters). IPH and ED use were measured for 6 months after the first overuse date (cohorts 2 and 3) or a randomly assigned date (cohort 1). Logistic regression analyses controlled for pre-treatment IPH/ED utilization, indication, addiction diagnosis, concomitant sedative/hypnotic use, and demographics.

Results: All-cause and drug-related IPH/ED utilization increased monotonically with degree of overuse, particularly of more than one medication. Sustained overuse of gabapentin multiplied odds of all-cause IPH by 1.366 [95% confidence interval (CI) 1.055–1.769], drug-related IPH by 1.440 (95% CI 1.010–2.053), and IPH/ED for altered mental status (e.g., euphoria, anxiety) by 1.864 (95% CI 1.324–2.624). Sustained overuse of both medications quadrupled odds of all-cause IPH, drug-related IPH, and IPH/ED for altered mental status or respiratory depression.

Conclusion: Despite modest effects of gabapentin overuse alone, overuse of gabapentin with opioids may increase risk of harm and health-service utilization, supporting calls to make gabapentin a controlled substance in the USA.

Erlotinib plus Bevacizumab Phase ll Study in Patients with Advanced Non-small-Cell Lung Cancer (JO25567): Updated Safety Results

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ABSTRACT

Introduction: The phase II JO25567 study compared the efficacy and safety of erlotinib plus bevacizumab vs. erlotinib alone as first-line therapy for advanced epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC).

Objective: Our objective is to provide updated analyses of safety and the assessment of manageability of specific adverse events.

Methods: Patients with stage IIIB/IV or recurrent, non-squamous, EGFR mutation-positive NSCLC were randomized to receive erlotinib plus bevacizumab or erlotinib. The primary endpoint was progression-free survival. Adverse event frequency rates, predictability and manageability, reasons for discontinuation, time to onset, and outcomes of specific adverse events were analyzed.

Results: The safety analysis population comprised 152 randomized patients (75 erlotinib plus bevacizumab; 77 erlotinib) who received at least one dose of study drug between February 2011 and March 2012. There was no difference in overall incidence of serious adverse events between arms, but more grade 3 or higher adverse events were reported with erlotinib plus bevacizumab (90.7%) than with erlotinib (53.2%), primarily due to grade 3 hypertension. Hypertension was controllable with antihypertensive medications in most cases. Proteinuria and bleeding were also more frequently reported with erlotinib plus bevacizumab than with erlotinib but were manageable and did not lead to early discontinuations.

Conclusions: The addition of bevacizumab to erlotinib prolonged progression-free survival in EGFR mutation-positive NSCLC. Follow-up safety data were consistent with the known safety profiles of both erlotinib and bevacizumab in NSCLC; this combination appeared to be manageable, and treatment was well tolerated.

Can SGLT2 Inhibitors Cause Acute Renal Failure? Plausible Role for Altered Glomerular Hemodynamics and Medullary Hypoxia

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ABSTRACT

Sodium–glucose co-transporter-2 inhibitors (SGLT2i) provide outstanding long-term cardiovascular and renal protection in high-risk patients with type 2 diabetes mellitus. Yet, despite encouraging renal safety outcomes reported in the EMPA-REG study, scattered reports suggest that there might be a risk for acute kidney injury (AKI), which may occasionally be fatal or might require renal replacement therapy. Reduced trans-glomerular pressure with a modest decline in kidney function, an inherent characteristic of SGLT2i therapy, conceivably forms the basis for the long-term renal protection, resembling agents that block the renin–angiotensin–aldosterone (RAAS) axis. Yet, a major decline in kidney function occasionally occurs, often associated with an acute illness or with specific co-administered medications. SGLT2i may lead to AKI by (a) effective volume depletion, due to excessive diuresis, particularly in hemodynamically unstable and volume-depleted patients; (b) excessive decline in trans-glomerular pressure, specifically in patients on RAAS blockade; and (c) induction of renal medullary hypoxic injury, related to enhanced distal tubular transport, especially with concomitant use of agents impairing medullary oxygenation, such as non-steroidal anti-inflammatory drugs and radiocontrast agents. The risk of developing renal impairment with SGLT2i and the role of these suggested mechanisms are yet to be defined, as there are conflicting data and inconsistent reporting with the various agents currently in use.

Neuropsychiatric Events Associated with Leukotriene-Modifying Agents: A Systematic Review

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ABSTRACT

Introduction: Leukotriene-modifying agents (LTMAs) including montelukast, zafirlukast, and zileuton are approved by the US Food and Drug Administration (FDA) for the treatment of asthma and allergic rhinitis. Various neuropsychiatric events (NEs) have been reported; however, the evidence of the association is conflicting. This systematic review investigates the association between NEs and LTMAs by assessing the relevant published literature.

Methods: PubMed, EMBASE, MEDLINE, and Cochrane Library were searched using keywords. Studies designed to investigate the association were eligible for inclusion without restriction to any study design or language. The primary outcome was defined as suicidal conditions, while secondary outcomes included all other NEs.

Results: Thirty-three studies were included for a narrative review. Four observational studies did not find a significant association, while ten pharmacovigilance studies using different global databases detected the signals. Notably, some studies suggest that the FDA warning issued in 2008 might have influenced the reporting rate of NEs as a result of increased awareness.

Limitations: The risk of NEs was not quantified, because of the lack of randomized controlled trials and observational studies investigating the association.

Conclusion: Many pharmacovigilance studies have been conducted to determine the association between NEs and LTMAs, but there is limited evidence from observational studies. High-quality epidemiological studies should be conducted to evaluate the association and quantify the risk, not only in children, but also in adults.

Utilisation and Safety of Deferasirox: Results from an Observational Cohort Study in England

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ABSTRACT

Introduction: Deferasirox (EXJADE®, Novartis, UK) is an oral iron-chelating agent primarily used to reduce chronic iron overload in patients receiving blood transfusions for various chronic anaemias and some non-transfusion dependant anaemias.

Objective: The aim of this study was to examine the utilisation and safety of deferasirox used in general practice in England.

Method: A single exposure observational cohort study design was used. Patients were identified from dispensed prescriptions for deferasirox between September 2006 and September 2014. Outcome data were collected via postal questionnaires sent to prescribers ≥ 6 months after first dispensed prescription for an individual patient. Summary descriptive statistics were calculated.

Results: The evaluable cohort consisted of 122 patients, of which 41.8% were aged 2–17 years. Frequent reasons for prescribing were sickle cell anaemia (27/103 where specified, 26.2%) and beta thalassaemia (26, 25.2%). The majority of patients (43/51, 84.3%) were prescribed the licensed doses of 10 or 20 mg/kg/day at start. Prior measurements of serum creatinine were only reported for a small proportion this study (18/122, 14.8%). In total, 91 incident events were reported, including two of raised serum creatinine.

Conclusion: These results show that deferasirox is largely being prescribed for its licensed indications in general practice in England and events reported were consistent with the known safety profile.

Severe Physical Complications among Survivors of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

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ABSTRACT

Introduction: Few studies have reported the physical complications among Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) survivors.

Objective: The aim of this study was to comprehensively characterize the physical complications among SJS/TEN survivors and to learn about patients' perspectives of surviving SJS/TEN.

Methods: SJS/TEN survivors older than 18 years of age were assessed by different methods: a medical interview; a questionnaire assessing patients' perspectives; thorough skin, oral mucous membrane, and ophthalmic examinations; and a retrospective assessment of medical records.

Results: Our cohort consisted of 17 patients with a mean time of 51.6 ± 74.7 months (median 9, range 1–228) following SJS/TEN. The most common physical complications identified in the medical examination were post-inflammatory skin changes (77%), cutaneous scars (46%), dry eyes (44%), symblepharon, and chronic ocular surface inflammation (33% each). Novel physical sequelae included chronic fatigue (76%) and pruritus (53%). We also found a novel association between the number of mucous membranes affected in the acute phase of SJS/TEN and hair loss during the 6 months following hospital discharge; hair loss was reported in 88% of the group of patients who had three or more mucous membranes affected versus 29% of patients who had less than three mucous membranes involved ($p = 0.0406$). Following hospital discharge due to SJS/TEN, 59% of patients were followed by a dermatologist, although 88% had dermatological complications; 6% were followed by an ophthalmologist, even though 67% had ophthalmological complications; and 6% of female survivors were followed by a gynecologist, even though 27% had gynecological complications.

Conclusion: Survivors of SJS/TEN suffer from severe physical complications impacting their health and lives that are mostly under recognized and not sufficiently treated by medical professionals.

Risk of Psoriasis Following Terbinafine or Itraconazole Treatment for Onychomycosis: A Population-Based Case-Control Comparative Study

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ABSTRACT

Introduction: Several case studies have reported an association between antifungal drug use and psoriasis risk.

Objective: The objective of this study was to investigate the association between terbinafine/itraconazole exposure and psoriasis incidence.

Methods: Among patients with onychomycosis in the Taiwan National Health Insurance Research Database, 3831 incident psoriasis cases were identified during 2004–2010 and compared with 3831 age- and sex-matched controls with the same look-back period. Multivariate conditional logistic regression was used for the analysis.

Results: The psoriasis cases were significantly more likely than matched controls to have used terbinafine or itraconazole (59.85 vs. 42.70%, respectively; $p < 0.0001$). After adjusting for potential confounders and cumulative duration of antifungal drug prescription, terbinafine/itraconazole use was associated with an increased psoriasis risk (adjusted odds ratio 1.33, 95% confidence interval 1.15–1.54). The association was stronger for more recent drug exposure (adjusted odds ratio 2.96, 95% confidence interval 2.25–3.90 for ≤ 90 days before the sampling date; adjusted odds ratio 1.04, 95% confidence interval 0.89–1.22 for > 360 days). In a comparison of patients receiving terbinafine or itraconazole only, psoriasis risk was higher for itraconazole (adjusted odds ratio 1.21, 95% confidence interval 1.05–1.40).

Conclusion: This large population-based case-control analysis showed that exposure to terbinafine or itraconazole is associated with an increased risk of incident psoriasis. The finding of an increased psoriasis risk for antifungal drug users, particularly for itraconazole, deserves attention in clinical practice although further prospective studies are necessary to confirm our findings and clarify the biological mechanisms that underlie these associations.

Evaluation of 'Definite' Anaphylaxis Drug Allergy Alert Overrides in Inpatient and Outpatient Settings

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ABSTRACT

Introduction: Drug–allergy interaction (DAI) alerts are generated when a known adverse sensitivity-inducing substance is prescribed. A recent study at our institution showed that providers overrode most DAI alerts, including those that warned against potentially life-threatening 'anaphylaxis'.

Objective: The aim of this study was to determine the rate of anaphylaxis overrides, the reasons for these overrides, whether the overrides were appropriate, and if harm occurred from overrides.

Methods: All DAI alerts, with a reaction of 'anaphylaxis', were analysed for inpatients and outpatients within our health system between January 2009 and December 2011. Only alerts that were triggered by 'definite' alerts (i.e. same ordered medication as documented allergen) were included. Patient charts were reviewed to assess the appropriateness of overrides and potential harm, according to a predetermined set of criteria.

Results: A total of 202 inpatient and 16 outpatient alerts met the inclusion criteria. The rate of overrides for 'definite' anaphylaxis DAI alerts was high (inpatient: n = 93, 46.0%; outpatient: n = 11, 68.8%) but appropriate for most overrides in the inpatient (n = 78, 83.9%) and outpatient settings (n = 11, 100%). The most common override reasons in the inpatient and outpatient settings were 'administer per desensitization protocol' (n = 64, 31.7%) and 'patient does not have this allergy' (n = 7, 63.6%), respectively. No harm was associated with overrides in either setting, particularly because many medications were not administered.

Conclusions: Overrides of 'definite' anaphylaxis DAI alerts were common and often appropriate. Most overrides were due to desensitizations. Allergy reconciliation for patients could further improve critical decision support.

Using Human 'Experiments of Nature' to Predict Drug Safety Issues: An Example with PCSK9 Inhibitors

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ABSTRACT

Introduction: When a new drug enters the market, its full array of side effects remains to be defined. Current surveillance approaches targeting these effects remain largely reactive. There is a need for development of methods to predict specific safety events that should be sought for a given new drug during development and postmarketing activities.

Objective: We present here a safety signal identification approach applied to a new set of drug entities, inhibitors of the serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9).

Methods: Using phenome-wide association study (PheWAS) methods, we analyzed available genotype and clinical data from 29,722 patients, leveraging the known effects of changes in PCSK9 to identify novel phenotypes in which this protein and its inhibitors may have impact.

Results: PheWAS revealed a significantly reduced risk of hypercholesterolemia (odds ratio [OR] 0.68, $p = 7.6 \times 10{-}4$) in association with a known loss-of-function variant in PCSK9, R46L. Similarly, laboratory data indicated significantly reduced beta mean low-density lipoprotein cholesterol ($-$ 14.47 mg/dL, $p = 2.58 \times 10{-}23$) in individuals carrying the R46L variant. The R46L variant was also associated with an increased risk of spina bifida (OR 5.90, $p = 2.7 \times 10{-}4$), suggesting that further investigation of potential connections between inhibition of PCSK9 and neural tube defects may be warranted.

Conclusion: This novel methodology provides an opportunity to put in place new mechanisms to assess the safety and long-term tolerability of PCSK9 inhibitors specifically, and other new agents in general, as they move into human testing and expanded clinical use.

Reported Adverse Events with Painkillers: Data Mining of the US Food and Drug Administration Adverse Events Reporting System

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ABSTRACT

Introduction: One-third of adults in the USA experience chronic pain and use a variety of painkillers, such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids. However, some serious adverse events (AEs), such as cardiovascular incidents, overdose, and death, have been found to be related to painkillers.

Methods: We used 2015 and 2016 AE reports from the US FDA's Adverse Events Reporting System (FAERS) to conduct exploratory analysis on the demographics of those who reported painkiller-related AEs, examine the AEs most commonly associated with different types of painkillers, and identify potential safety signals. Summary descriptive statistics and proportional reporting ratios (PRRs) were performed.

Results: Out of over 2 million reports submitted to FAERS in 2015 and 2016, a total of 64,354 AE reports were associated with painkillers. Reports of opioid-associated AEs were more likely to be from males or younger patients (mean age 47.6 years). The highest numbers of AEs were reported for NSAID and opioid use, and the most commonly found AEs were related to drug ineffectiveness, administration issues, abuse, and overdose. Death was reported in 20.0% of the reports, and serious adverse reactions, including death, were reported in 67.0%; both adverse outcomes were highest among patients using opioids or combinations of painkillers and were associated with PRRs of 2.12 and 1.87, respectively.

Conclusions: This study examined the AEs most commonly associated with varying classes of painkillers by mining the FAERS database. Our results and methods are relevant for future secondary analyses of big data and for understanding adverse outcomes related to painkillers.

Management Strategies to Facilitate Optimal Outcomes for Patients Treated with Delayed-release Dimethyl Fumarate

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ABSTRACT

Delayed-release dimethyl fumarate is an oral disease-modifying therapy that has demonstrated significant efficacy in adults with relapsing–remitting multiple sclerosis. Incidences of flushing and gastrointestinal adverse events are common in the first month after delayed-release dimethyl fumarate initiation. Our objective was to propose mitigation strategies for adverse events related to initiation of delayed-release dimethyl fumarate in the treatment of patients with multiple sclerosis. Studies of individually developed mitigation strategies and chart reviews were evaluated. Those results, as well as mitigation protocols developed at multiple sclerosis care centers, are summarized. Key steps to optimize the effectiveness of delayed-release dimethyl fumarate treatment include education prior to and at the time of delayed-release dimethyl fumarate initiation, initiation dose protocol gradually increasing to maintenance dose, dietary suggestions for co-administration with food, gastrointestinal symptom management with over-the-counter medications, flushing symptom management with aspirin, and temporary dose reduction. Using the available evidence from clinical trials and evaluations of post-marketing studies, these strategies to manage gastrointestinal and flushing symptoms can be effective and helpful to the patient when initiating delayed-release dimethyl fumarate.

Analysis of Spontaneous Postmarket Case Reports Submitted to the FDA Regarding Thromboembolic Adverse Events and JAK Inhibitors

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ABSTRACT

Introduction: The Janus kinase (JAK) inhibitor baricitinib is approved in Europe and Japan for the treatment of rheumatoid arthritis. In April 2017, the US FDA expressed concern about thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]) observed in placebo-controlled clinical trials of baricitinib. The European and Japanese labels for baricitinib were recently updated to include a precaution related to potential thromboembolic events in patients at risk. Given that the FDA-approved drugs tofacitinib and ruxolitinib are in the same class, we conducted a safety review of the FDA's Adverse Event Reporting System (FAERS) to assess postmarketing reporting rates for related thromboembolic risks.

Methods: Adverse event (AE) data for tofacitinib, tofacitinib extended-release (XR), and ruxolitinib were obtained from the FAERS. Reporting odds ratios (RORs) and the R package 'PhViD' to estimate the empirical Bayesian geometric mean (EBGM) were used to detect AEs with higher-than-expected reporting rates within the FAERS.

Results: We did not find evidence in the FAERS for elevated reporting rates for DVT and PE across the three JAK inhibitors we analyzed. However, multiple drug–AE combinations relating to thromboembolic events had both RORs and EBGM values above 1, indicating a trend toward higher-than-expected reporting rates. For pulmonary thrombosis, the ROR values for ruxolitinib, tofacitinib, and tofacitinib XR were 1.46 (95% confidence interval [CI] 0.76–2.80), 2.46 (1.55–3.91), and 2.48 (0.80–7.71), respectively, while the EBGM values were 1.25 (0.70), 2.46 (1.64), and 1.56 (0.57), respectively. Ruxolitinib had ROR values of 4.08 (2.25–7.38) and 1.22 (0.97–1.53) for portal vein thrombosis and thrombosis, respectively. The EBGM values for the same drug–AE combinations were 3.04 (1.79) and 1.16 (0.96).

Conclusions: Our safety review of postmarketing FAERS reports associated with three FDA-approved JAK inhibitors did not find elevated reporting rates for DVT and PE specifically. However, the FAERS data indicated that pulmonary thrombosis may potentially be a class-wide issue for JAK inhibitors. Portal vein thrombosis may also be a potential risk for ruxolitinib. While these FAERS data add to a growing body of evidence that JAK inhibitors may be contraindicated in patients at risk of thromboembolic events, the data need to be confirmed by future AE reporting trends, analysis of electronic health records, and/or future clinical trials.

Mixed Approach Retrospective Analyses of Suicide and Suicidal Ideation for Brand Compared with Generic Central Nervous System Drugs

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ABSTRACT

Introduction: Several different types of drugs acting on the central nervous system (CNS) have previously been associated with an increased risk of suicide and suicidal ideation (broadly referred to as suicide). However, a differential association between brand and generic CNS drugs and suicide has not been reported.

Objectives: This study compares suicide adverse event rates for brand versus generic CNS drugs using multiple sources of data.

Methods: Selected examples of CNS drugs (sertraline, gabapentin, zolpidem, and methylphenidate) were evaluated via the US FDA Adverse Event Reporting System (FAERS) for a hypothesis-generating study, and then via administrative claims and electronic health record (EHR) data for a more rigorous retrospective cohort study. Disproportionality analyses with reporting odds ratios and 95% confidence intervals (CIs) were used in the FAERS analyses to quantify the association between each drug and reported suicide. For the cohort studies, Cox proportional hazards models were used, controlling for demographic and clinical characteristics as well as the background risk of suicide in the insured population.

Results: The FAERS analyses found significantly lower suicide reporting rates for brands compared with generics for all four studied products (Breslow–Day $P < 0.05$). In the claims- and EHR-based cohort study, the adjusted hazard ratio (HR) was statistically significant only for sertraline (HR 0.58; 95% CI 0.38–0.88).

Conclusion: Suicide reporting rates were disproportionately larger for generic than for brand CNS drugs in FAERS and adjusted retrospective cohort analyses remained significant only for sertraline. However, even for sertraline, temporal confounding related to the close proximity of black box warnings and generic availability is possible. Additional analyses in larger data sources with additional drugs are needed.

An Automated System Combining Safety Signal Detection and Prioritization from Healthcare Databases: A Pilot Study

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ABSTRACT

Introduction: Signal detection from healthcare databases is possible, but is not yet used for routine surveillance of drug safety. One challenge is to develop methods for selecting signals that should be assessed with priority.

Aim: The aim of this study was to develop an automated system combining safety signal detection and prioritization from healthcare databases and applicable to drugs used in chronic diseases.

Methods: Patients present in the French EGB healthcare database for at least 1 year between 2005 and 2015 were considered. Noninsulin glucose-lowering drugs (NIGLDs) were selected as a case study, and hospitalization data were used to select important medical events (IME). Signal detection was performed quarterly from 2008 to 2015 using sequence symmetry analysis. NIGLD/IME associations were screened if one or more exposed case was identified in the quarter, and three or more exposed cases were identified in the population at the date of screening. Detected signals were prioritized using the Longitudinal-SNIP (L-SNIP) algorithm based on strength (S), novelty (N), and potential impact of signal (I), and pattern of drug use (P). Signals scored in the top 10% were identified as of high priority. A reference set was built based on NIGLD summaries of product characteristics (SPCs) to compute the performance of the developed system.

Results: A total of 815 associations were screened and 241 (29.6%) were detected as signals; among these, 58 (24.1%) were prioritized. The performance for signal detection was sensitivity = 47%; specificity = 80%; positive predictive value (PPV) 33%; negative predictive value = 82%. The use of the L-SNIP algorithm increased the early identification of positive controls, restricted to those mentioned in the SPCs after 2008: PPV = 100% versus PPV = 14% with its non-use. The system revealed a strong new signal with dipeptidylpeptidase-4 inhibitors and venous thromboembolism.

Conclusion: The developed system seems promising for the routine use of healthcare data for safety surveillance of drugs used in chronic diseases.

The RIMES Statement: A Checklist to Assess the Quality of Studies Evaluating Risk Minimization Programs for Medicinal Products

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ABSTRACT

Introduction: Pharmaceutical risk minimization programs involve interventions designed to support safe and appropriate use of medicines. Currently, information regarding the evaluation of these programs is not publicly reported in a standardized and transparent manner. To address this gap, we developed and piloted a quality reporting checklist entitled the Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies (RIMES).

Methods: Checklist development was guided by three sources: (1) a theoretical framework derived from program theory and process evaluation; (2) public health intervention design and evaluation principles; and (3) a review of existing quality reporting checklists. Two raters independently reviewed 10 recently published (2012–2016) risk minimization program evaluation studies using the proposed checklist. Inter-rater reliability of the checklist was assessed using Cohen's Kappa and Gwet's AC1.

Results: A 43-item checklist was generated. Results indicated substantial inter-rater reliability overall ($\kappa = 0.65$, AC1 = 0.65) and for three (key information, design and evaluation) of the four subscales ($\kappa \geq 0.64$, AC1 ≥ 0.64). The fourth subscale (implementation) showed low reliability based on Cohen's Kappa, but substantial reliability based on the AC1 ($\kappa = 0.17$, AC1 = 0.61).

Conclusions: The RIMES statement augments relevant elements from existing quality reporting guidelines with items that address aspects of intervention design, implementation and evaluation specific to pharmaceutical risk minimization programs. Our results show that the RIMES statement reliably measures key dimensions of reporting quality. This tailored checklist is an important first step in improving the reporting quality of risk minimization evaluation studies and may ultimately help to improve the quality of these interventions themselves.

Amyotrophic Lateral Sclerosis Associated with Statin Use: A Disproportionality Analysis of the FDA's Adverse Event Reporting System

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ABSTRACT

Introduction: Apparent elevations in reporting of amyotrophic lateral sclerosis (ALS)-like conditions associated with statin use have been previously described from data obtained via US and European databases.

Objective: The aim of this study was to examine US FDA Adverse Event Reporting System (FAERS) data to compare reporting odds ratios (RORs) of ALS and ALS-like conditions between statins and other drugs, for each statin agent.

Methods: We assessed for disproportional rates of reported ALS and ALS-related conditions for each statin agent separately by using the ROR formula. FAERS data were analyzed through September 2015.

Results: RORs for ALS were elevated for all statins, with elevations possibly stronger for lipophilic statins. RORs ranged from 9.09 (6.57–12.6) and 16.2 (9.56–27.5) for rosuvastatin and pravastatin (hydrophilic) to 17.0 (14.1–20.4), 23.0 (18.3–29.1), and 107 (68.5–167) for atorvastatin, simvastatin, and lovastatin (lipophilic), respectively. For simvastatin, an ROR of 57.1 (39.5–82.7) was separately present for motor neuron disease.

Conclusion: These findings extend previous evidence showing that significantly elevated ALS reporting extends to individual statin agents, and add to concerns about potential elevated occurrence of ALS-like conditions in association with statin usage.

Beta-Blocker Use in Pregnancy and Risk of Specific Congenital Anomalies: A European Case-Malformed Control Study

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ABSTRACT

Introduction: The prevalence of chronic hypertension is increasing in pregnant women. Beta-blockers are among the most prevalent anti-hypertensive agents used in early pregnancy.

Objective: The objective of this study was to investigate whether first-trimester use of beta-blockers increases the risk of specific congenital anomalies in offspring.

Methods: A population-based case-malformed control study was conducted in 117,122 registrations of congenital anomalies from 17 European Concerted Action on Congenital Anomalies and Twins (EUROCAT) registries participating in EUROmediCAT with data for all or part of the period between 1995 and 2013. Associations previously reported in the literature (signals) were tested and an exploratory analysis was performed to identify new signals. Odds ratios of exposure to any beta-blocker or to a beta-blocker subgroup were calculated for each signal anomaly compared with two control groups (non-chromosomal, non-signal anomalies and chromosomal anomalies). The exploratory analyses were performed for each non-signal anomaly compared with all the other non-signal anomalies.

Results: The signals from the literature (congenital heart defects, oral clefts, neural tube defects and hypospadias) were not confirmed. Our exploratory analysis revealed that multi-cystic renal dysplasia had significantly increased odds of occurring after maternal exposure to combined alpha- and beta-blockers (adjusted odds ratio 3.8; 95% confidence interval 1.3–11.0).

Conclusion: Beta-blocker use in the first trimester of pregnancy was not found to be associated with a higher risk of specific congenital anomalies in the offspring, but a new signal between alpha- and beta-blockers and multi-cystic renal dysplasia was found. Future large epidemiological studies are needed to confirm or refute our findings.

Cardiovascular Profile of Valbenazine: Analysis of Pooled Data from Three Randomized, Double-Blind, Placebo-Controlled Trials

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ABSTRACT

Introduction: Valbenazine is a novel vesicular monoamine transporter 2 inhibitor approved for the treatment of tardive dyskinesia in adults.

Objective: Using data from double-blind, placebo-controlled trials, analyses were conducted to evaluate the cardiovascular effects of once-daily valbenazine in patients with a psychiatric disorder who developed tardive dyskinesia after exposure to a dopamine-blocking medication.

Methods: Data were pooled from three 6-week, double-blind, placebo-controlled trials: KINECT (NCT01688037), KINECT 2 (NCT01733121), and KINECT 3 (NCT02274558). Data from the 42-week valbenazine extension period of KINECT 3 were also analyzed. Outcomes of interest included cardiovascular-related treatment-emergent adverse events, vital sign measurements, and electrocardiogram parameters.

Results: The pooled safety population included 400 participants (placebo, n = 178; valbenazine 40 mg/day, n = 110; valbenazine 80 mg/day, n = 112). A history of cardiac disorders was present in 11.8% of participants, and 74.3% were taking a concomitant medication with known potential for QT prolongation. Mean changes from baseline to week 6 in supine vital signs and QTcF (Fridericia correction) were as follows for placebo, valbenazine 40 mg/day, and valbenazine 80 mg/day, respectively: systolic blood pressure (0.2, − 2.1, − 1.8 mmHg), diastolic blood pressure (− 0.1, − 1.6, − 1.2 mmHg), heart rate (− 1.7, − 2.2, − 1.7 bpm), QTcF interval (1.2, 1.1, 2.1 ms); all $p > 0.05$ for valbenazine vs. placebo. No statistically significant differences were observed between placebo and valbenazine in cardiovascular-related, treatment-emergent adverse events. No notable additional effects on cardiovascular outcomes were found with up to 48 weeks of valbenazine treatment.

Conclusions: Results from double-blind, placebo-controlled trials showed no apparent difference between valbenazine and placebo on cardiovascular outcomes. No additional cardiovascular risk was detected during a longer extension study with valbenazine.

Long-Acting β2-Agonists in Asthma: Enantioselective Safety Studies are needed

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ABSTRACT

Long-acting β2-agonists (LABAs) such as formoterol and salmeterol are used for prolonged bronchodilatation in asthma, usually in combination with inhaled corticosteroids (ICSs). Unexplained paradoxical asthma exacerbations and deaths have been associated with LABAs, particularly when used without ICS. LABAs clearly demonstrate effective bronchodilatation and steroid-sparing activity, but long-term treatment can lead to tolerance of their bronchodilator effects. There are also concerns with regard to the effects of LABAs on bronchial hyperresponsiveness (BHR), where long-term use is associated with increased BHR and loss of bronchoprotection. A complicating factor is that formoterol and salmeterol are both chiral compounds, usually administered as 50:50 racemic (rac-) mixtures of two enantiomers. The chiral nature of these compounds has been largely forgotten in the debate regarding LABA safety and effects on BHR, particularly that (S)-enantiomers of β2-agonists may be deleterious to asthma control. LABAs display enantioselective pharmacokinetics and pharmacodynamics. Biological plausibility of the deleterious effects of β2-agonists (S)-enantiomers is provided by in vitro and in vivo studies from the short-acting β2-agonist (SABA) salbutamol. Supportive clinical findings include the fact that patients in emergency departments who demonstrate a blunted response to salbutamol are more likely to benefit from (R)-salbutamol than rac-salbutamol, and resistance to salbutamol appears to be a contributory mechanism in rapid asthma deaths. More effort should therefore be applied to investigating potential enantiospecific effects of LABAs on safety, specifically bronchoprotection. Safety studies directly assessing the effects of LABA (S)-enantiomers on BHR are long overdue.

Drug-Induced Ototoxicity: Diagnosis and Monitoring

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ABSTRACT

Ototoxicity diagnosis and management has historically been approached using a variety of methods. However, in recent years a consensus on useful and practical approaches has been developed through clinical guidelines of the American Speech Language Hearing Association, the American Academy of Audiology, and multiple clinical trials published in peer-reviewed literature. Some of the guidelines and approaches are used to detect and monitor ototoxicity, while others are used to grade adverse events. Some of the audiologic measures are primary, while others are adjunct measures and may be tailored to the specific needs of the patient or clinical trial. For some types of monitoring, such as drug-induced tinnitus or dizziness, validated paper survey instruments can be both sensitive and easy for fragile patients. This review addresses the characteristics of some of the most common clinical ototoxins and the most common methods for detecting and monitoring ototoxicity in clinical practice and clinical trials.

A Review of Methods for Monitoring Adverse Events in Pediatric Psychopharmacology Clinical Trials

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ABSTRACT

Pediatric psychotropic prescription rates are rising, emphasizing the need for careful monitoring of drug safety in this population. Currently, no standardized assessments are used in clinical trials for adverse event (AE) elicitation focused on long-term drug treatment in pediatric patients. Despite a lack of standardized AE elicitation methods in psychiatric clinical trials, it is clear that psychiatric medications have developmentally dependent AEs that differ from those observed in adults. In this review, we discuss the use of general inquiry elicitation, drug-specific checklists, and systematic elicitation scales for AE reporting in pediatric psychopharmacology trials. The checklists evaluated include the Barkley Side Effect Rating Scales (SERS), the Pittsburg side effect rating scale, and the Systematic Monitoring of Adverse events Related to TreatmentS (SMARTS) checklist. The systematic assessment scales discussed include the Systematic Assessment for Treatment of Emergent Events (SAFTEE) and the Safety Monitoring Uniform Report Form (SMURF). We review the advantages and disadvantages of each method and discuss the need for optimal assessment of AEs. AE instruments that are created and utilized for pediatric psychiatric trials must begin to incorporate symptoms that are relevant to this population and account for the nature of the disorders to better characterize treatment-emergent AEs and monitor long-term safety.

The Impact of Biologics and Tofacitinib on Cardiovascular Risk Factors and Outcomes in Patients with Rheumatic Disease: A Systematic Literature Review

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ABSTRACT

Introduction: Rheumatic diseases are autoimmune, inflammatory diseases often associated with cardiovascular (CV) disease, a major cause of mortality in these patients. In recent years, treatment with biologic and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs), either as monotherapy or in combination with other drugs, have become the standard of treatment. In this systematic literature review, we evaluated the effect of treatment with biologic or tofacitinib on the CV risk and outcomes in these patients.

Methods: A systematic search was performed in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for articles reporting on CV risk and events in patients with rheumatic disease treated with a biologic agent or tofacitinib. Articles identified were subjected to two levels of screening. Articles that passed the first level based on title and abstract were assessed on full-text evaluation. The quality of randomized clinical trials was assessed by Jadad scoring system and the quality of the other studies and abstracts was assessed using the Downs and Black instrument. The data extracted included study design, baseline patient characteristics, and measurements of CV risk and events.

Results: Of the 5722 articles identified in the initial search, screening yielded 105 unique publications from 90 unique studies (33 clinical trials, 39 prospective cohort studies, and an additional 18 retrospective studies) that reported CV risk outcomes. A risk of bias analysis for each type of report indicated that they were of good or excellent quality. Importantly, despite some limitations in data reported, there were no indications of significant increase in adverse CV events or risk in response to treatment with the agents evaluated.

Conclusions: Treatment with biologic or tofacitinib appears to be well-tolerated with respect to CV outcomes in these patients.

Potential Risks Related to Modulating Interleukin-13 and Interleukin-4 Signalling: A Systematic Review

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ABSTRACT

Introduction: Interleukin-13 and interleukin-4 are type-II cytokines signalling through the shared type II interleukin-4 receptor. As a result of their structural similarity, interleukin-13 and interleukin-4 have overlapping functions in the mediation of type-II-driven diseases and are, therefore, promising targets of biologic drugs currently in development for the treatment of such diseases, including asthma and atopic dermatitis.

Objective: This systematic review was conducted to assess preclinical evidence of potential safety concerns related to blockade of interleukin-13 alone or interleukin-13 and interleukin-4 in combination.

Methods: We specifically examined risks related to infection, malignancy and the cardiovascular system. We systematically searched the BIOSIS, MEDLINE and EMBASE databases to identify preclinical studies published between January 2006 and October 2016 that addressed the effects of interleukin-13/interleukin-4 blockade and modulation on the risk of infection, malignancy and cardiovascular events. To provide a clinical context, we also performed a search for clinical trials targeting the interleukin-13/interleukin-4 pathways. Relevant data from preclinical and clinical trials were abstracted and presented descriptively.

Results: Aside from expected evidence that inhibition of interleukin-13 and interleukin-4 impaired host responses to helminth infections, we did not identify other preclinical evidence suggesting safety risks relating to infection, malignancy or cardiovascular events. We found no evidence in clinical trials suggesting serious safety concerns, i.e. increased risk for infections, malignancy or cardiovascular events from therapeutic modulation of the interleukin-13 pathway alone or the combined interleukin-13/interleukin-4 pathways.

Conclusions: Although our findings are reassuring, long-term safety assessments of biologics that target the interleukin-13/interleukin-4 pathways currently in clinical development are needed.

Adverse Drug Reaction Reports Received Through the Mobile App, VigiBIP®: A Comparison with Classical Methods of Reporting

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ABSTRACT

Introduction: The use of mobile apps is increasing in medicine. In pharmacovigilance, mobile apps may help to increase adverse drug reaction reporting and improve the communication of safety issues. The Toulouse University Pharmacovigilance Center has developed VigiBIP®, a free smartphone app available on Android and Apple stores, for reporting adverse drug reactions and requesting drug safety information.

Objective: The present study was performed to compare the main characteristics of spontaneous adverse drug reaction reports received through VigiBIP® with classical methods of reporting (phone, e-mail, fax, letter, website) during 25 months (2015–17).

Methods: Using the Chi squared test, we compared the type of reporter, adverse drug reaction seriousness, drugs involved and reported ADRs using VigiBIP® and classical methods of reporting

Results: A total of 4102 reports were received by the Toulouse University Pharmacovigilance Center, including 4.7% through VigiBip®. Patients' reports were significantly more frequent with VigiBip® (6.7%) than with classical methods (3.4%) [p = 0.01]. Reported adverse drug reactions and involved drugs differed according to the method of reporting used.

Conclusion: Our study shows that a mobile app is an additional tool used in pharmacovigilance. Types of reporters and adverse drug reactions in VigiBIP were different to those seen in classical methods of reporting.

Case Series Analysis of New Zealand Reports of Rapid Intense Potentiation of Warfarin by Roxithromycin

Ruth L. Savage, Michael V. Tatley

ABSTRACT

Introduction: We undertook an analysis of all the reports to the New Zealand Centre for Adverse Reactions Monitoring of a roxithromycin/warfarin interaction after two recent reports described intense rapid warfarin potentiation. The interaction was first published in 1995. Cytochrome P450 3A4 inhibition has been the proposed mechanism but has limited biologic plausibility. There are suggestions that the clinical significance of the interaction may be increased by severe illness, polypharmacy, renal dysfunction, older age and increased warfarin sensitivity.

Methods: To investigate the potentiating effect of warfarin on roxithromycin in this New Zealand case series, the reports were reviewed to identify patients at risk, compare the reporting pattern with published Australian data and evaluate the appropriateness of current prescribing advice.

Results: Thirty patient reports were identified. The age range was 23–88 years, mean 66.8, median 73.0 (standard deviation 17.7) and the international normalised ratios after roxithromycin commencement ranged from 3.6 to 16.7 (mean 7.6, median 7.6, standard deviation 3.6). For eight patients with measurements on day 3, international normalised ratios were 4.3–16.7 (mean 10.4, median 8.8, standard deviation 4.4). Four patients had serious haemorrhage. Indications for roxithromycin were a range of respiratory tract infections. Anticoagulation was stable for most patients prior to acute infection. Serious infection occurred in 54.5% (12 of 22 patients with information). Polypharmacy (five or more medicines daily) was used by 36.7% of patients long term, increasing acutely to 83.3%, including additional potentially interacting medicines. Warfarin daily dose (1.5–13.0 mg, mean 4.4, median 4.0, standard deviation 2.2) was moderate to low. Pre-roxithromycin international normalised ratio values ranged from 1.4 to 3.7, mean and median 2.5, standard deviation 0.5. A high proportion of interactions were observed between warfarin and roxithromycin compared with other macrolides and compared with cytochrome P450 3A4-related macrolide interactions. The pattern was similar to published Australian data.

Conclusion: In this case series, the high prevalence of acute polypharmacy, including potentially interacting medicines, and serious infection suggests that they may have contributed to warfarin potentiation and increased the clinical significance of a roxithromycin/warfarin interaction.

Signal Detection for Recently Approved Products: Adapting and Evaluating Self-Controlled Case Series Method Using a US Claims and UK Electronic Medical Records Database

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ABSTRACT

Introduction: The Self-Controlled Case Series (SCCS) method has been widely used for hypothesis testing, but there is limited evidence of its performance for safety signal detection.

Objective: The objective of this study was to evaluate SCCS for signal detection on recently approved products.

Methods: A retrospective study covered the period after three recently marketed drugs were launched through to 31 December 2010 using The Health Improvement Network, a UK primary care database, and Optum, a US claims database. The SCCS method was applied to examine five heterogenous outcomes with desvenlafaxine and escitalopram and six outcomes with adalimumab for Signals of Disproportional Recording (SDRs); a positive finding was determined to be when the lower bound of 95% Confidence Interval of the incidence rate ratio (IRR) estimate was > 1. Multiple design choices were tested and the trend in IRR estimates over calendar time for one drug event pair was examined.

Results: All six outcomes with adalimumab, three of five outcomes with desvenlafaxine, and four of five outcomes with escitalopram had SDRs. SCCS highlighted all acute events in the primary analysis but was less successful with slower-onset outcomes. Performance varied by risk period definition. Changes in IRR estimates over quarterly intervals for adalimumab with herpes zoster showed marked higher SDR within 9 months of drug launch.

Conclusion: SCCS shows promise for signal detection: it may highlight known associations for recent marketed products and has potential for early signal identification. SCCS performance varied by design choice and the nature of both exposure and event pair. Future work is needed to determine how effective the approach is in prospective testing and determining the performance characteristics of the approach.

Gastrointestinal Perforations with Biologics in Patients with Rheumatoid Arthritis: Implications for Clinicians

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ABSTRACT

Gastrointestinal (GI) perforations are rare events in rheumatoid arthritis (RA) patients, but cause significant morbidity and mortality. Several studies indicate that RA patients may be at higher risk of GI perforation. Traditional RA treatments such as glucocorticoids and non-steroidal anti-inflammatory drugs increase the risk of perforation. In the past two decades, a new class of therapeutic agents called biologics has been added to the RA treatment armamentarium. Biologics are effective in controlling disease activity and are generally well tolerated; however, reports of GI perforations in association with biologics have arisen. In particular, drugs that inhibit the interleukin (IL)-6 cytokine receptor have demonstrated a higher risk of perforation compared with other therapies. Recent reports also suggest that janus kinase inhibitors may increase the risk of perforation, perhaps via downstream effects on IL-6 signaling. In this review, we discuss current data on the risk of GI perforations among RA patients receiving targeted therapies and its clinical relevance.

The Risk for Lung Cancer Incidence with Calcium Channel Blockers: A Systematic Review and Meta-Analysis of Observational Studies

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Abstract

Introduction: There are conflicting findings regarding the association between the use of calcium channel blockers (CCBs) and the risk of lung cancer. Considering the public health importance of lung cancer prevention, and emerging evidence of a significant biologic role of calcium channel regulation in the development of lung cancer, we conducted a meta-analysis to assess the risk of lung cancer in CCB users compared with non-CCB users.

Materials and Methods: We conducted a comprehensive systematic search of leading medical databases for observational studies published up to December 2017 that examined CCB use and the risk of lung cancer. We used random-effects models to pool results. The impact of duration of CCB use on the estimated effect size was explored using random effects meta-regression.

Results: Ten studies (six cohort and four case–control studies) that evaluated the overall cancer risk among 38,758 CCB users were included in the analysis. Overall risk ratio (RR) for CCB use and lung cancer was 1.15 (95% confidence interval [CI] 1.01–1.32). Subgroup analysis by duration of CCB use suggested that the observed increase in lung cancer risk was driven by the results of five studies with prolonged (≥ 4 years) exposure (RR 1.18; 95% CI 1.08–1.30).

Conclusions: Our analysis suggests exposure to CCBs is associated with an increased risk of lung cancer. Considering their widespread use, and the paucity of data on the long-term effects of chronic exposure to CCBs, these results are reason for concern and warrant further investigation.

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

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ABSTRACT

Introduction: Signal detection remains a cornerstone activity of pharmacovigilance. Routine quantitative signal detection primarily focuses on screening of spontaneous reports. In striving to enhance quantitative signal detection capability further, other data streams are being considered for their potential contribution as sources of emerging signals, one of which is longitudinal observational databases, including electronic medical record (EMR) and transactional insurance claims databases. Quantitative signal detection on such databases is a nascent field—with published methods being primarily based either on individual metrics, which may not effectively represent the complexity of the longitudinal records and their necessary variation for analysis for drug–outcome pairs, or on visualization discovery approaches leveraging multiple aspects of the records, which are not particularly tractable to high-throughput hypothesis-free signal detection. One extensively tested example of the latter is chronographs.

Methods: We apply a disturbance detection algorithm to chronographs using UK EMR The Health Improvement Network (THIN) data. The algorithm utilizes autoregressive integrated moving average (ARIMA)-based time series methodology designed to find disturbances that occur outside the normal pattern trends of the ARIMA model for the chronograph. Chronographs currently highlight drug–event pairs as potentially worthy of further clinical assessment, via filter-based increases in disproportionality scores from before to after the index drug exposure, tested across a range of case and control windows.

Results: We replicate the findings on six exemplar chronographs from a previous publication, and show how disturbances can be effectively detected across this set of pairs. Further, 692 disturbances were detected in analysis of all 384 individual READ code outcomes ever recorded 50 or more times for patients prescribed sibutramine. The disturbances are algorithmically further broken into subsets of clinical interest.

Conclusion: Overall, the disturbance algorithm approach shows promising capacity for detecting outliers, and shows tractability of the algorithmic approach for large-scale screening. The method offers an array of pattern types for detection and clinical review.

Sorting Through the Safety Data Haystack: Using Machine Learning to Identify Individual Case Safety Reports in Social-Digital Media

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ABSTRACT

Introduction: There is increasing interest in social digital media (SDM) as a data source for pharmacovigilance activities; however, SDM is considered a low information content data source for safety data. Given that pharmacovigilance itself operates in a high-noise, lower-validity environment without objective 'gold standards' beyond process definitions, the introduction of large volumes of SDM into the pharmacovigilance workflow has the potential to exacerbate issues with limited manual resources to perform adverse event identification and processing. Recent advances in medical informatics have resulted in methods for developing programs which can assist human experts in the detection of valid individual case safety reports (ICSRs) within SDM.

Objective: In this study, we developed rule-based and machine learning (ML) models for classifying ICSRs from SDM and compared their performance with that of human pharmacovigilance experts.

Methods: We used a random sampling from a collection of 311,189 SDM posts that mentioned Roche products and brands in combination with common medical and scientific terms sourced from Twitter, Tumblr, Facebook, and a spectrum of news media blogs to develop and evaluate three iterations of an automated ICSR classifier. The ICSR classifier models consisted of sub-components to annotate the relevant ICSR elements and a component to make the final decision on the validity of the ICSR. Agreement with human pharmacovigilance experts was chosen as the preferred performance metric and was evaluated by calculating the Gwet AC1 statistic (gKappa). The best performing model was tested against the Roche global pharmacovigilance expert using a blind dataset and put through a time test of the full 311,189-post dataset.

Results: During this effort, the initial strict rule-based approach to ICSR classification resulted in a model with an accuracy of 65% and a gKappa of 46%. Adding an ML-based adverse event annotator improved the accuracy to 74% and gKappa to 60%. This was further improved by the addition of an additional ML ICSR detector. On a blind test set of 2500 posts, the final model demonstrated a gKappa of 78% and an accuracy of 83%. In the time test, it took the final model 48 h to complete a task that would have taken an estimated 44,000 h for human experts to perform.

Conclusion: The results of this study indicate that an effective and scalable solution to the challenge of ICSR detection in SDM includes a workflow using an automated ML classifier to identify likely ICSRs for further human SME review.

A Multi-hospital Before–After Observational Study Using a Point-Prevalence Approach with an Infusion Safety Intervention Bundle to Reduce Intravenous Medication Administration Errors

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ABSTRACT

Introduction: We previously found a high rate of errors in the administration of intravenous medications using smart infusion pumps.

Objectives/Design: An infusion safety intervention bundle was developed in response to the high rate of identified errors. A before–after observational study with a prospective point-prevalence approach was conducted in nine hospitals to measure the preliminary effects of the intervention.

Main Outcome Measures: Primary outcome measures were overall errors and medication errors, with the secondary outcome defined as potentially harmful error rates.

Results: We assessed a total of 418 patients with 972 medication administrations in the pre-intervention period and 422 patients with 1059 medication administrations in the post-intervention period. The overall error rate fell from 146 to 123 per 100 medication administrations ($p < 0.0001$), and the medication error rate also decreased from 39 to 29 per 100 medication administrations ($p = 0.001$). However, there was no significant change in the potentially harmful error rate (from 0.5 to 0.8 per 100 medication administrations, $p = 0.37$). An intervention component aiming to reduce labeling-not-completed errors was effective in reducing targeted error rates, but other components of the intervention bundle did not show significant improvement in the targeted errors.

Conclusion: Development and implementation of the intervention bundle was successful at reducing overall and medication error rates, but some errors remained and the potentially harmful error rate did not change. The error-rate reductions were not always correlated with the specific individual interventions. Further investigation is needed to identify the best strategies to reduce the remaining errors.

Evidence-Based Recommendations to Improve the Safe Use of Drugs in Patients with Liver Cirrhosis

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ABSTRACT

Introduction: The presence of liver cirrhosis can have a major impact on pharmacodynamics and pharmacokinetics, but guidance for prescribing is lacking.

Objective: The aim of this study is to provide an overview of evidence-based recommendations developed for the safe use of drugs in liver cirrhosis.

Methods: Recommendations were based on a systematic literature search combined with expert opinion from a panel of 10 experts. The safety of each drug was classified as safe, no additional risks known, additional risks known, unsafe, unknown or the safety class was dependent on the severity of liver cirrhosis (Child–Pugh classification). If applicable, drug-specific dosing advice was provided. All recommendations were implemented in clinical decision support systems and on a website.

Results: We formulated 218 recommendations for a total of 209 drugs. For nine drugs, two recommendations were formulated for different administration routes or indications. Drugs were classified as ‘safe’ in 29 recommendations (13.3%), ‘no additional risks known’ in 60 (27.5%), ‘additional risks known’ in 3 (1.4%), and ‘unsafe’ in 30 (13.8%). In 57 (26.1%) of the recommendations, safety depended on the severity of liver cirrhosis and was ‘unknown’ in 39 (17.9%) recommendations. Large alterations in pharmacodynamics were the main reason for classifying a drug as ‘unsafe’. For 67 drugs (31%), a dose adjustment was needed.

Conclusions: Over 200 recommendations were developed for the safe use of drugs in patients with liver cirrhosis. Implementing these recommendations into clinical practice can possibly enhance medication safety in this vulnerable patient group.

The Uncertainty of the Association between Proton Pump Inhibitor Use and the Risk of Dementia: Prescription Sequence Symmetry Analysis Using a Korean Healthcare Database between 2002 and 2013

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ABSTRACT

Introduction: Studies have found an association between the use of proton pump inhibitors (PPIs) and dementia, but these findings may have been confounded by selection biases.

Objective: We used prescription sequence symmetry analysis (PSSA) to estimate the sequence ratio (SR) between PPI use and dementia compared with an active comparator, the use of histamine-2 receptor antagonists (H2RAs).

Methods: We conducted a PSSA on a nationwide South Korean database between 2002 and 2013. Exposure was defined as new PPI users, and outcome was defined as a new dementia diagnosis (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] codes F00-03, F05.1, G30, G31.1, G31.9, G31.82). In this study, we applied the 3-year time window. So the patients who initiated PPIs 3 years before or after their first diagnosis of dementia were included. The pairs with the time window < 6 months were excluded to minimize the potential protopathic bias. The SR was calculated as the number of patients first diagnosed with dementia after initiating PPI (causal group) divided by the number of patients first diagnosed with dementia before the initiation of PPI (non-causal group). The SR was adjusted (aSR) to avoid the distortion of results due to underlying trends in PPI use and dementia diagnosis over time. We calculated 95% confidence intervals (CIs) for the aSR. The analysis was repeated for initiators of H2RAs. Sensitivity analyses were conducted using 1-, 2-, and 6-year time windows and using the initiation of medication for dementia treatment (Anatomical Therapeutic Chemical code: N06D).

Results: Our results showed that the aSR of dementia and PPIs (7342 pairs, aSR 1.21 [95% CI 1.16–1.27]) was not higher than that for dementia and H2RAs (6170 pairs, aSR 1.91 [95% CI 1.80–2.02]). When we used various time windows and restricted the findings to the use of medication for treating dementia, the results were consistent with the main results.

Conclusion: The risk of PPIs being associated with dementia may be overestimated. Further pharmacoepidemiological studies are needed to identify the risk of dementia with PPI use.

Liver Safety of Fasiglifam (TAK-875) in Patients with Type 2 Diabetes: Review of the Global Clinical Trial Experience

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ABSTRACT

Introduction: Fasiglifam (TAK-875) is a G protein-coupled receptor 40 agonist that was being investigated for treatment of type 2 diabetes mellitus (T2DM). A development program was terminated late in phase III clinical trials due to liver safety concerns.

Methods: The liver safety of fasiglifam was assessed from data based on six phase II and nine phase III double-blind studies and two open-label studies with emphasis on pooled data from 15 double-blind studies from both global and Japanese development programs. Taking into consideration different daily doses of fasiglifam administered in clinical studies, the primary comparisons were between all patients exposed to fasiglifam (any dose) versus placebo, and, where applicable, versus the two active comparators, sitagliptin or glimepiride. A Liver Safety Evaluation Committee consisting of hepatologists blinded to treatment assignments evaluated hepatic adverse events (AEs) and serious AEs (SAEs) for causal relationship to study drug.

Results: The analysis included data from 9139 patients with T2DM in 15 double-blind controlled studies who received either fasiglifam (n = 5359, fasiglifam group), fasiglifam and sitagliptin (n = 123), or a comparator agent (n = 3657, non-exposed group consisting of placebo and other antidiabetic agents). Exposure to treatment for more than 1 year ranged from 249 patients in the placebo arm, to 370 patients in the glimepiride arm and 617 patients in the fasiglifam 50 mg arm. The primary focus of the analysis was on the hepatic safety of fasiglifam. The overall safety profile based on treatment-emergent AEs (TEAEs), SAEs, deaths, and withdrawal due to AEs was similar between fasiglifam and placebo (excluding liver test abnormalities). However, there was an increased incidence rate of serum alanine aminotransferase (ALT) elevations > 3 × upper limit of normal (ULN), 5 × ULN, and 10 × ULN in fasiglifam-treated patients compared with those treated with placebo or active comparators. ALT elevations > 3 × ULN for fasiglifam were 2.7% compared with 0.8 and 0.5% for the active comparators and placebo. There did not appear to be a clear dose response in incidence of ALT elevations between patients receiving 25 or 50 mg daily. The cumulative incidence of elevations in serum ALT > 3 × ULN was higher in the first 6 months of treatment with fasiglifam compared with both placebo and the active comparators, but the rate of new ALT elevations appeared to be similar across all treatment groups thereafter. No demographic or baseline patient characteristics were identified to predict elevations exceeding ALT > 3 × ULN in fasiglifam-treated patients. The pattern of liver injury with fasiglifam was hepatocellular, and there were no reports of liver-related deaths, liver failure or life-threatening liver injury. Most fasiglifam-associated ALT elevations were asymptomatic and resolved promptly upon discontinuing treatment, but in two patients the recovery was prolonged. Importantly, three important serious liver injury cases were identified among fasiglifam-treated patients; one case was adjudicated to be a clear Hy's Law case and the two remaining cases were considered to closely approximate Hy's Law cases.

Conclusions: Although the incidence of overall AEs, SAEs, and deaths was similar between fasiglifam and placebo, a liver signal was identified based primarily on the difference in liver chemistry values in the fasiglifam group compared with the placebo and active comparator groups. Three serious liver injuries were attributed to fasiglifam treatment. Clinical development of fasiglifam was halted due to these liver safety concerns.

Thromboembolism with Janus Kinase (JAK) Inhibitors for Rheumatoid Arthritis: How Real is the Risk?

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ABSTRACT

Two different Janus kinase (JAK) inhibitors—baricitinib and tofacitinib—are effective and licensed in active rheumatoid arthritis (RA). There have been recent concerns about potential thromboembolic risks with these drugs. Concerns about baricitinib focus on clinical trial findings. Using all publically available data, we estimate thromboembolic risks are approximately five events per 1000 patient years with 4 mg baricitinib daily. Concerns about tofacitinib have been raised by analyses of the Federal Drug Administration Adverse Event Reporting System (FAERs). These show some evidence of increased risks of pulmonary thrombosis, though not pulmonary embolism or venous thrombosis. Observational studies suggest in the general population and non-RA controls there are one to four thromboembolic events per 1000 patient years. In RA, thromboembolic risks increase to three to seven per 1000 patient years. The impact of biologics and disease-modifying anti-rheumatic drugs (DMARDs) on disease risk appears minimal, and the number of thromboembolic events is between four and eight per 1000 patient years. In the short term, full details of thromboembolic events in trials of JAK inhibitors need to be published. As the numbers of thromboembolic events will be small and patients enrolled in trials are not representative of all RA patients who may receive JAK inhibitors, this information is unlikely to provide definitive answers. Consequently, in the longer term, large observational studies are needed to accurately quantify thromboembolic risks attributable to JAK inhibitors and other drugs used to treat RA, and differentiate these from risks attributable to RA itself and its comorbidities.

Limited Evidence for Risk Factors for Proarrhythmia and Sudden Cardiac Death in Patients Using Antidepressants: Dutch Consensus on ECG Monitoring

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ABSTRACT

Currently, there is a lack of international and national guidelines or consensus documents with specific recommendations for electrocardiogram (ECG) screening and monitoring during antidepressant treatment. To make a proper estimation of the risk of cardiac arrhythmias and sudden (cardiac) death during antidepressant use, both the drug and patient-specific factors should be taken into account; however, solid evidence on how this should be done in clinical practice is lacking. Available recommendations on the management of QT(c) prolongation (with antidepressant treatment) emphasize that special attention should be given to high-risk patients; however, clinicians are in need of more concrete suggestions about how to select patients for ECG screening and monitoring. Based on a review of the literature, a Dutch multidisciplinary expert panel aimed to formulate specific guidelines to identify patients at risk for cardiac arrhythmias and sudden death by developing a consensus statement regarding ECG screening before, and monitoring during, antidepressant use. We first reviewed the literature to identify the relative risks of various risk factors on cardiac arrhythmia and sudden (cardiac) death during antidepressant use. These relative contributions of risk factors could not be determined since no systematic reviews or meta-analyses quantitatively addressed this topic. Because evidence was insufficient, additional expert opinion was used to formulate recommendations. This resulted in readily applicable recommendations for clinical practice for selection of high-risk patients for ECG screening and monitoring. ECG screening and monitoring is recommended before and following the start of QTc-prolonging antidepressants in the presence of vulnerability to QTc prolongation or two or more risk factors (age > 65 years, female sex, concomitant use of a QTc-prolonging drug or concomitant use of a drug that influences the metabolism of a QTc-prolonging drug, cardiac disease, excessive dosing and specific electrolyte disturbances).

EudraVigilance Medicines Safety Database: Publicly Accessible Data for Research and Public Health Protection

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ABSTRACT

The analysis of safety data from spontaneous reporting systems has a proven value for the detection and analysis of the risks of medicines following their placement on the market and use in medical practice. EudraVigilance is the pharmacovigilance database to manage the collection and analysis of suspected adverse reactions to medicines authorised in the European Economic Area. EudraVigilance first operated in December 2001, with access to the database being governed by the EudraVigilance access policy. We performed a literature search including data up to December 2016 to demonstrate how the data from EudraVigilance has been used in scientific publications. We describe the results, including by type of publication, research topics and drugs involved. In 50% of the publications, the data are used to describe safety issues, in 44% to analyse methodologies used in pharmacovigilance activities and in 6% to support clinical perspectives. We also outline a description of the use of the database by the European Union regulatory network. Driven by the full implementation of the 2010 pharmacovigilance legislation, EudraVigilance has undergone further enhancements together with a major revision of its access policy, taking into account the use of the new individual case safety report standard developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and the International Organization for Standardization. The aim of the broadened access is to facilitate more effective safety monitoring of authorised medicines, to make more data available for research and to provide better access to information on suspected adverse reactions for healthcare professionals and patients. In November 2017, the new full functionalities of EudraVigilance were launched, including the extensive web access to data on suspected adverse drug reactions and the possibilities for academic research institutions to request a more extensive dataset for the purposes of health research. The main objective of this article is to describe the new access to the database together with the opportunities that this new access can bring for research. It is intended to promote an appropriate use of the data to support the safe and effective use of medicines.

Sex Differences in Reported Adverse Drug Reactions of Selective Serotonin Reuptake Inhibitors

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ABSTRACT

Introduction: Several studies have investigated sex as a risk factor for the occurrence of adverse drug reactions (ADRs) and found that women are more likely to experience ADRs than men.

Objective: The aim of this explorative study was to investigate whether differences exist in reported ADRs of Selective Serotonin Reuptake Inhibitors (SSRIs) for men and women in the database of the Netherlands Pharmacovigilance Centre Lareb.

Methods: A ratio of reports concerning women and men, corrected for the number of users, was calculated for all the ADRs reported on SSRIs.

Results: We found that 16 ADRs were statistically significantly more reported in women than men, and four ADRS were reported more in men than women.

Conclusion: ADRs more reported in women than men when using SSRIs were usually dose-related ADRs or commonly occurring ADRs. Differences in the pharmacokinetics of SSRIs between men and women may explain why these reports of dose-related ADRs when using SSRIs concern women more than men.

Using the Symmetry Analysis Design to Screen for Adverse Effects of Non-vitamin K Antagonist Oral Anticoagulants

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ABSTRACT

Introduction: Knowledge on adverse effects (AEs) related to non-vitamin K antagonist oral anticoagulants (NOACs) in real-world populations is sparse.

Objective: Our objective was to identify signals of potential AEs in patients with atrial fibrillation (AF) initiating NOAC treatment using a hypothesis-free screening approach.

Methods: Using the nationwide Danish registries, we identified patients with AF initiating dabigatran, rivaroxaban, or apixaban between 2011 and 2015 (n = 50,627). Applying a symmetry analysis design, we screened for AEs of NOAC, as reflected by new drug treatments, incident diagnoses, or procedures. For signals with the lowest number needed for one additional patient to be harmed (NNTH), we evaluated whether they likely represented genuine AEs or other types of associations. Signals assessed as potential AEs were grouped into five categories for analysis of effect modification according to patient and drug characteristics.

Results: Of the identified signals, 61 were classified as potential AEs. Most signals could be categorized as the following types of AEs: bleedings, non-bleeding gastrointestinal symptoms, mental disease, urinary tract disorders, and musculoskeletal symptoms. Older age and first-ever use of anticoagulants was associated with strengthening of all "NOAC-adverse effect" associations. Conversely, use of low-dose NOAC and apixaban led to attenuation of most associations.

Conclusion: Through a symmetry analysis-based hypothesis-free screening of large-scale healthcare databases, we were able to confirm well-established AEs of NOAC therapy in clinical practice as well as potential AEs that deserve further investigation.

Interest in a Mobile App for Two-Way Risk Communication: A Survey Study among European Healthcare Professionals and Patients

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ABSTRACT

Introduction: Previously, an app has been developed for healthcare professionals (HCPs) and patients to report adverse drug reactions (ADRs) to national medicines agencies and to receive drug safety information.

Objective: This study aimed to assess (1) European HCPs' and patients' interest in an app for this two-way risk communication; (2) their preferences and perceptions towards specific app characteristics; and (3) which HCPs and patients are particularly interested in the app. In addition, these aspects were studied specifically for the countries where such an app was already available, i.e. Croatia, The Netherlands, and The UK.

Methods: European HCPs and patients were asked to complete a web-based survey developed in the context of the Web-Recognizing Adverse Drug Reactions (Web-RADR) project. Data on app interest and preferences and perceptions towards app characteristics were analysed descriptively. Logistic regression analyses were conducted to assess the association of HCP characteristics and patient characteristics on the level of interest in the app (i.e. very interested vs. not/somewhat interested).

Results In total, 399 HCPs and 656 patients completed the survey. About half of the patients (48%; ranging from 38% from The Netherlands to 54% from The UK), and 61% of the HCPs (ranging from 42% from The Netherlands to 54% from The UK) were very interested in the app. A faster means of reporting ADRs and easier access to the reporting form were the main perceived benefits. HCPs and patients who already use a health app were particularly interested in the app (HCPs: odds ratio [OR] 3.52; 95% confidence interval [CI] 1.96–6.30, patients: OR 1.64; 95% CI 1.19–2.27).

Conclusions: An app is positively perceived by HCPs and patients for reporting ADRs quickly and for receiving drug safety information from national medicines agencies. In particular, HCPs and patients who already use other health apps were interested in the app.

Safety Communication Tools and Healthcare Professionals' Awareness of Specific Drug Safety Issues in Europe: A Survey Study

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ABSTRACT

Introduction: National competent authorities (NCAs) use Direct Healthcare Professional Communications (DHPCs) to communicate new drug safety issues to healthcare professionals (HCPs). More knowledge is needed about the effectiveness of DHPCs and the extent to which they raise awareness of new safety issues among HCPs.

Objective: The objective was to assess and compare general practitioners' (GPs'), cardiologists', and pharmacists' familiarity with DHPCs as communication tools, their awareness of specific drug safety issues, and the sources through which they had become aware of the specific issues.

Methods: GPs, cardiologists, and pharmacists from nine European countries (Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and the UK) completed a web-based survey. The survey was conducted in the context of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. Respondents were asked about their familiarity with DHPCs in general and their awareness of safety issues that had recently been communicated and involved the following drugs: combined hormonal contraceptives, diclofenac, valproate, and ivabradine. Those HCPs who were aware of the specific safety issues were subsequently asked to indicate the source through which they had become aware of them. Differences between professions in familiarity with DHPCs and awareness were tested using a Pearson $\chi 2$ test per country and post hoc Pearson $\chi 2$ tests in the case of statistically significant differences.

Results: Of the 3288 included respondents, 54% were GPs, 40% were pharmacists, and 7% were cardiologists. The number of respondents ranged from 67 in Denmark to 916 in Spain. Most respondents (92%) were familiar with DHPCs, with one significant difference between the professions: pharmacists were more familiar than GPs in Italy (99 vs 90%, P = 0.004). GPs' awareness ranged from 96% for the diclofenac issue to 70% for the ivabradine issue. A similar pattern was shown for pharmacists (91% aware of the diclofenac issue to 66% of the ivabradine issue). Cardiologists' awareness ranged from 91% for the ivabradine issue to 34% for the valproate issue. Overall, DHPCs were a common source through which GPs (range: 45% of those aware of the contraceptives issue to 60% of those aware of the valproate issue), cardiologists (range: 33% for the contraceptives issue to 61% for the valproate issue), and pharmacists (range: 41% for the contraceptives issue to 51% for the ivabradine issue) had become aware of the specific safety issues, followed by information on websites or in newsletters.

Conclusions: GPs, cardiologists, and pharmacists were to a similar extent (highly) familiar with DHPCs, but they differed in awareness levels of specific safety issues. Cardiologists were less aware of safety issues associated with non-cardiology drugs even if these had cardiovascular safety concerns. This implies that additional strategies may be needed to reach specialists when communicating safety issues regarding drugs outside their therapeutic area but with risks related to their field of specialisation. DHPCs were an important source for the different professions to become aware of specific safety issues, but other sources were also often used. NCAs should consider the use of a range of sources when communicating important safety issues to HCPs.

Glucocorticoids and the Risk of Peptic Ulcer Bleeding: Case–Control Analysis Based on Swiss Claims Data

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ABSTRACT

Introduction: Controversy exists as to whether glucocorticoids (GC) are ulcerogenic per se and may thus cause peptic ulcer bleeding (PUB) independent of concomitantly prescribed nonsteroidal anti-inflammatory drugs (NSAIDs).

Objective: To investigate the association between GC use and PUB with or without co-medication with NSAIDs.

Methods: We conducted a case–control study using administrative claims data from the Swiss health insurance company Helsana. We identified 1191 cases with incident PUB between 2012 and 2016 and matched up to 10 PUB-free controls to each case on age, sex, region and number of years insured with Helsana. We compared prior GC exposure between cases and controls using multivariate conditional logistic regression analyses controlling for several potential confounders. Patients with or without concomitant NSAID exposure were analysed separately.

Results: Patients with prior exposure to both GC and NSAIDs were five times more likely to experience PUB than patients who neither used GC nor NSAIDs (adjusted odds ratio [adj. OR] 4.80, 95% CI 3.55–6.71). Although the risk of PUB among patients who used NSAIDs without GC was increased threefold (adj. OR 3.20, 95% CI 2.59–3.95), we observed only a moderately increased risk among patients who used GC alone without NSAIDs (adj. OR 1.63, 95% CI 1.20–2.42).

Conclusions: The use of NSAIDs with or without GC was associated with a markedly higher risk of PUB compared with GC monotherapy. Use of GC alone was associated with a moderately increased risk of PUB, which might be causal or attributed to confounding by indication.

Drug-Induced Liver Injury: Why is the Roussel Uclaf Causality Assessment Method (RUCAM) still used 25 Years after Its Launch?

Gaby Danan, Rolf Teschke

ABSTRACT

Launched in 1993 and partially based on the results of an international consensus meeting organized under the auspices of the Council of International Organizations of Medical Sciences (CIOMS), the Roussel Uclaf Causality Assessment Method (RUCAM) is the most used causality assessment tool worldwide for the diagnosis of drug-induced liver injury (DILI) and herb-induced liver injury (HILI) in a large number of epidemiological studies, case reports, and case series. The 25-year experience of RUCAM use confirmed that the success was due to its objective, standardized, and liver-injury-specific approach structured with defined key elements derived from a series of DILI cases with positive rechallenge. Using this series, the validation procedure avoided arbitrary definitions and confirmed scores to key items. The algorithm provides a quantitative causality grading of highly probable, probable, possible, unlikely, or excluded relationship between the liver injury and the suspected product(s). Despite challenges, prospective use of RUCAM fosters case data completeness and transparent causality adjudication in real time, as opposed to subjective opinion resulting from several rounds by experts lacking defined key elements and scores. In 2016, RUCAM was updated with specification of alcohol use and Hepatitis E Virus (HEV) biomarkers and simplified item handling to further reduce inter-observer variability. RUCAM-based probable and highly probable DILI and HILI cases are essential for the detection of new hepatotoxins, confirmation of new biomarkers, description of clinical features and risk factors, and determination of incidence in pharmacoepidemiological studies. This article is intended to encourage systematic use of sophisticated causality assessment methods such as RUCAM to improve DILI and HILI case evaluation and to increase confidence in published cases.

Adverse Events to Food Supplements Containing Red Yeast Rice: Comparative Analysis of FAERS and CAERS Reporting Systems

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ABSTRACT

Introduction: Food supplements containing red yeast rice (RYR) are proposed as an alternative in statin-intolerant patients, although they actually contain natural statin(s) and their safety in clinical practice is still incompletely characterized. We described and compared adverse events (AEs) associated with RYR products submitted to reporting systems maintained by the Food and Drug Administration (FDA), with a focus on liver and muscular events.

Methods: We extracted RYR-related AEs from the FDA Adverse Event Reporting System (FAERS) [first quarter (Q1)-2004 to Q2-2016], a drug-based archive, and the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS) (Q1-2004 to Q1-2017). Disproportionality via reporting odds ratio (ROR) with 95% confidence interval (CI) calculation and case-by-case inspection were performed, with a focus on muscular and hepatic AEs.

Results: One thousand three hundred AEs were extracted from FAERS (RYR mainly reported as a concomitant agent), whereas only 159 AEs were found in CAERS (RYR recorded mainly as a suspect agent). In FAERS, a large number of reports emerged for "general disorders and administration site conditions," whereas CAERS received also a high number of reports for "investigations" and "musculoskeletal and connective tissue disorders". Disproportionality analyses confirmed higher reporting of serious muscular and liver injuries: in FAERS, five cases of hepatic disorders (ROR = 13.71; 95% CI 5.44–34.57); in CAERS, 27 cases of rhabdomyolysis/myopathy (8.44; 5.44–13.10).

Conclusions: Notwithstanding recognized limitations, these findings strengthen the importance of exploring multiple databases in safety assessment of RYR products, which should be monitored by clinicians for muscular and hepatic safety, and call for urgent review by policymakers to harmonize their regulatory status.

The Burden of Adverse Drug Reactions Due to Artemisinin-Based Antimalarial Treatment in Selected Ugandan Health Facilities: An Active Follow-Up Study

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ABSTRACT

Introduction: Uganda has rapidly increased access to antimalarial medicines in an effort to address the huge malaria disease burden. Pharmacovigilance information is important to guide policy decisions.

Objectives: The purpose of this study was to establish the burden of adverse drug reactions (ADRs) and associated risk factors for developing ADRs to artemisinin-based antimalarial treatment in Uganda.

Methods: An active follow-up study was conducted between April and July 2017 in a cohort of patients receiving treatment for uncomplicated malaria in the Iganga, Mayuge, and Kampala districts.

Results: A total of 782 patients with a median age of 22 years (58.6% females) were recruited into this study, with the majority recruited from public health facilities (97%). Diagnostic tests before treatment were performed for 76% of patients, and 97% of patients received artemether/lumefantrine. The prevalence of ADRs was 22.5% (176/782); however, the total number of ADRs was 245 since some patients reported more than one ADR. The most commonly reported reactions were general body weakness (24%), headache (13%), and dizziness (11%). Women were more likely to develop an ADR (adjusted odds ratio [aOR] 1.8, 95% confidence interval [CI] 1.1–2.9), urban dwellers were more likely to develop an ADR than rural residents (aOR 9.9, 95% CI 5.4–17.9), and patients with comorbidities were more likely to develop an ADR than those without (aOR 7.4, 95% CI 4.4–12.3).

Conclusion: The burden of ADRs is high among women and in patients from urban settings and those with comorbidities. Such risk factors need to be considered in order to optimise therapy. Close monitoring of ADRs is key in implementation of the malaria treatment policy.

Central Demyelinating Diseases after Vaccination against Hepatitis B Virus: A Disproportionality Analysis within the VAERS Database

Julie Mouchet, Bernard Bégaud

ABSTRACT

Introduction: Hepatitis B (HB) vaccination programs were set up worldwide in the early 1990s. Despite their major focus on reducing the burden of HB infection, they have seldom achieved the targeted population coverage in most countries, including the USA, with around 24.5% of adults being vaccinated against HB. Among proposed reasons for this is the persisting doubt about a possible link between HB vaccination and the occurrence of cases of multiple sclerosis (MS).

Objective: Our objective was to evaluate a potential safety signal between MS and HB vaccination. We conducted a disproportionality analysis (DPA) using the cases reported to the Vaccine Adverse Event Reporting System (VAERS).

Methods: We calculated the proportional reporting rate (PRR) and reporting odds ratio (ROR) of MS having occurred within the 120 days following HB immunization in adults aged 19–49 years when compared with other vaccines using the reports recorded in the VAERS database. Both ratios were estimated globally and then according to the origin of reports (USA vs. non-USA). We then performed a sensitivity analysis using a broader category of demyelinating events.

Findings: MS cases following HB vaccination were more likely to originate from outside the USA and to be reported before 2000 than those associated with other immunizations. All computed ratios were found to be statistically significant, with PRRs ranging from 3.48 to 5.56 and RORs ranging from 3.48 to 5.62. When considering the geographical origin, similar RORs were obtained for both US and non-US cases.

Conclusion: In VAERS, MS cases were up to five times more likely to be reported after an HB vaccination than after any other vaccination. Since DPA is mainly suited for hypothesis generation, further studies evaluating the nature of the link between MS and HB vaccination would be of considerable importance.

Benefit–Risk Monitoring of Vaccines Using an Interactive Dashboard: A Methodological Proposal from the ADVANCE Project

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ABSTRACT

Introduction: New vaccines are launched based on their benefit–risk (B/R) profile anticipated from clinical development. Proactive post-marketing surveillance is necessary to assess whether the vaccination uptake and the B/R profile are as expected and, ultimately, whether further public health or regulatory actions are needed. There are several, typically not integrated, facets of post-marketing vaccine surveillance: the surveillance of vaccination coverage, vaccine safety, effectiveness and impact.

Objective: With this work, we aim to assess the feasibility and added value of using an interactive dashboard as a potential methodology for near real-time monitoring of vaccine coverage and pre-specified health benefits and risks of vaccines.

Methods: We developed a web application with an interactive dashboard for B/R monitoring. The dashboard is demonstrated using simulated electronic healthcare record data mimicking the introduction of rotavirus vaccination in the UK. The interactive dashboard allows end users to select certain parameters, including expected vaccine effectiveness, age groups, and time periods and allows calculation of the incremental net health benefit (INHB) as well as the incremental benefit–risk ratio (IBRR) for different sets of preference weights. We assessed the potential added value of the dashboard by user testing amongst a range of stakeholders experienced in the post-marketing monitoring of vaccines.

Results: The dashboard was successfully implemented and demonstrated. The feedback from the potential end users was generally positive, although reluctance to using composite B/R measures was expressed.

Conclusion: The use of interactive dashboards for B/R monitoring is promising and received support from various stakeholders. In future research, the use of such an interactive dashboard will be further tested with real-life data as opposed to simulated data.

Comparative Rates of Mortality and Serious Adverse Effects among Commonly Prescribed Opioid Analgesics

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ABSTRACT

Introduction: The epidemic of prescription opioid overdose and mortality parallels the dispensing rates of prescription opioids, and the availability of increasingly potent opioid analgesics.

Objective: The common assumption that more potent opioid analgesics are associated with higher rates of adverse outcomes has not been adequately substantiated. We compared the rate of serious adverse events among commonly prescribed opioid analgesics of varying potency.

Methods: Serious adverse events (SAEs; defined as death, major medical effect, or hospitalization) resulting from exposure to tablets containing seven opioid analgesics (oxycodone, hydrocodone, morphine, hydromorphone, oxymorphone, tapentadol, and tramadol) captured by the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program were evaluated from 2010 through 2016. Rates of SAEs were adjusted for availability through outpatient dispensing data and regressed on morphine milligram equivalents (MME).

Results: There were 19,480 cases of SAE during the 7-year study period. Hydrocodone and oxycodone contributed to 77% of SAE cases. Comparing rates of outcome by relative potency, a hierarchy was observed with hydromorphone (8.02 SAEs/100 kg) and tapentadol (0.27 SAE/100 kg) as the highest and lowest rates, reflecting a 30-fold difference among individual opioid products. SAE rate and potency were related linearly—SAEs increased 2.04 per 100 kg drug dispensed for each 1-unit rise in MME ($p = 0.004$). Linear regression of SAE/100 kg drug dispensed and drug potency identified that MME comprised 96% of the variation observed. In contrast, potency did not explain variation seen using other study denominators (prescriptions dispensed, dosage units dispensed, and the number of individuals filling a prescription).

Conclusions and Relevance: Potency of a prescription opioid analgesic demonstrates a significant, highly positive linear relationship with exposures resulting in SAEs per 100 kg drug dispensed reported to poison centers. Potency should be carefully considered from both individual provider and public health perspectives.

Effectiveness Evaluation of Additional Risk Minimization Measures for Adolescent Use of Aripiprazole in the European Union: Results from a Post-Authorization Safety Study

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ABSTRACT

Introduction: Two risk minimization (RM) tools—a healthcare professional frequently asked questions (HCP-FAQs) brochure and a patient/caregiver information brochure (PCIB)—were developed for HCPs and for adolescents (aged ≥ 13 years) receiving aripiprazole for bipolar I mania and their caregivers.

Objectives: This study evaluated the effectiveness of these RM tools in improving the awareness and education of HCPs and patients/caregivers.

Method: The RM tools were distributed to HCPs (identified in agreement with the marketing authorization holder [MAH] and local regulatory authorities), who in turn distributed the PCIBs to patients/caregivers. A web-based survey was then conducted targeting HCPs and patients/caregivers.

Results: The response rate was low: 118 of 23,282 invited HCPs and 16 patients/caregivers completed the survey. Overall, 42% (49/118) of HCP respondents were aware of aripiprazole RM tools; of these, 59% (29/49) of HCPs read them at least once and 66% (19/29) of these used the RM tools while discussing the benefit–risk profile of aripiprazole with patients/caregivers. In total, 30 of the 118 HCPs (25%) were aware of the PCIB, and 26 distributed it to their patients/caregivers, whereas seven HCPs advised them to read the brochure. Overall, 15 of the 16 patients/caregivers were aware of the PCIB, and 13 read/referred to it. Of these, 12 found the PCIB useful, and five monitored their weight while receiving aripiprazole and reported potential risks immediately to their HCP.

Conclusion: The response rate to the survey was low, and the tools displayed limited utility and effectiveness in improving awareness and education in a small number of responders. Therefore, the aripiprazole risk management plan was amended, and the tools were discontinued.

Programme for Risk Assessment and Minimisation of Progressive Multifocal Leukoencephalopathy Developed for Vedolizumab Clinical Trials

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ABSTRACT

Introduction: Over the past decade, the potential for drug-associated progressive multifocal leukoencephalopathy (PML) has become an increasingly important consideration in certain drug development programmes, particularly those of immunomodulatory biologics. Whether the risk of PML with an investigational agent is proven (e.g. extrapolated from relevant experience, such as a class effect) or merely theoretical, the serious consequences of acquiring PML require careful risk minimisation and assessment. No single standard for such risk minimisation exists. Vedolizumab is a recently developed monoclonal antibody to α4β7 integrin. Its clinical development necessitated a dedicated PML risk minimisation assessment as part of a global preapproval regulatory requirement.

Objective: The aim of this study was to describe the multiple risk minimisation elements that were incorporated in vedolizumab clinical trials in inflammatory bowel disease patients as part of the risk assessment and minimisation of PML programme for vedolizumab.

Methods: A case evaluation algorithm was developed for sequential screening and diagnostic evaluation of subjects who met criteria that indicated a clinical suspicion of PML. An Independent Adjudication Committee provided an independent, unbiased opinion regarding the likelihood of PML.

Results: Although no cases were detected, all suspected PML events were thoroughly reviewed and successfully adjudicated, making it unlikely that cases were missed.

Conclusion: We suggest that this programme could serve as a model for pragmatic screening for PML during the clinical development of new drugs.

Healthcare Databases for Drug Safety Research: Data Validity Assessment Remains Crucial

Nigel S. B. Rawson, Carl D'Arcy

ABSTRACT

Administrative healthcare utilization databases are frequently used either individually or as a component of aggregated data for evaluating drug safety issues without taking into account their known deficiencies. All too often insufficient evidence is provided about their validity for the purposes for which they are used. The assessment of data validity is a key constituent that should be included in drug safety research studies and should take a broad multifaceted approach that encompasses both diagnostic and drug exposure data. Drug safety researchers need to continue advancing their knowledge of the data resources they use and to ensure that they and the users of their research understand the limitations of the data that are the foundation on which their research is built. Fundamental issues regarding data validity should be addressed in each use of administrative data for drug safety research.

Safety of Tamsulosin: A Systematic Review of Randomized Trials with a Focus on Women and Children

Steven A. Kaplan, Bilal I. Chughtai

ABSTRACT

Introduction: Although tamsulosin is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH), it has also been assessed in clinical studies for other conditions/symptoms and in other populations such as women and children. In this systematic review of randomized studies, the overall safety of tamsulosin was assessed, focusing on these understudied populations.

Methods: Literature searches were conducted using Embase, Medline, and PubMed (inception–December 2015). A study was included if patients were randomized to receive treatment with any dose of tamsulosin capsules, tablets, or an oral controlled absorption system and numerical safety results were reported.

Results: Overall, 160 articles involving 46,072 participants met the inclusion criteria. Of these, four studies included women only and three included children. The mean [standard deviation (SD)] age ranged from 7.3 (4.2) to 76.8 (7.1) years. The studies (n; %) evaluated healthy subjects (18; 11%) or patients with lower urinary tract symptoms/BPH (90; 56%), ureteral stones/renal colic (42; 26%), prostatitis (4; 3%), or other conditions (6; 4%). Patients discontinued tamsulosin primarily because of adverse events (AEs) or insufficient response. AEs in women and children were abdominal pain, asthenia, constipation, dizziness, dry mouth, drowsiness, dyspepsia, headache, incontinence, nasal congestion, nausea, orthostatic hypotension, and somnolence. Due to heterogeneity across studies, statistical analysis could not be conducted.

Discussion: No unexpected AEs were observed in an all-comers population treated with tamsulosin for various conditions/symptoms. The overall safety profile in women and children seemed to be generally consistent with the profile in men, the indicated population.

Osteoporosis-Related Fractures in HIV-Infected Patients Receiving Long-Term Tenofovir Disoproxil Fumarate: An Observational Cohort Study

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ABSTRACT

Introduction: Patients with HIV infection may have a higher prevalence of osteoporosis and osteopenia, as well as an increased risk of bone fracture compared with non-HIV-infected individuals. Antiretroviral therapy is thought to be one of factors associated to osteoporosis-related bone fractures.

Objective: The aim of this study was to assess the effects of long-term exposure to tenofovir disoproxil fumarate (TDF) on the cumulative risk of osteoporosis-related bone fractures in Japanese patients with HIV infection.

Design: This observational cohort study comprised a joint HIV-related drug survey of patients treated with TDF between April 2004 and March 2013.

Methods: Thirty-five healthcare facilities in Japan participated in the survey. The incidence of osteoporosis-related fractures was extracted from all adverse events (AEs) using standardized Medical Dictionary for Regulatory Activities queries, and used to calculate the fracture rate per 10,000 patient-years (PY). Kaplan–Meier analysis was used to estimate the cumulative probability of fracture during the study period.

Results: A total of 3251 patients who received TDF or TDF/emtricitabine between April 2004 and March 2013 were analyzed in this study; 93.5% of patients were male. The fracture rate was 13.5 per 10,000 PY in males and 42.2 per 10,000 PY in females. The mean age for male patients with osteoporosis-related fracture was 43.2 years, whereas it was 65.7 years in female patients. The cumulative probability of osteoporosis-related fracture increased after ≥ 5 years of TDF exposure. The rate of hip fracture (95% confidence interval) was 7.2 (3.1–14.2) per 10,000 PY.

Conclusions: Among HIV-infected patients in Japan, treatment with TDF for ≥ 5 years increases the risk of bone fractures in younger men, in addition to that seen in older post-menopausal women.

Comparison of Data on Serious Adverse Events and Mortality in ClinicalTrials.gov, Corresponding Journal Articles, and FDA Medical Reviews: Cross-Sectional Analysis

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ABSTRACT

Introduction: Inconsistencies in data on serious adverse events (SAEs) and mortality in ClinicalTrials.gov and corresponding journal articles pose a challenge to research transparency.

Objective: The objective of this study was to compare data on SAEs and mortality from clinical trials reported in ClinicalTrials.gov and corresponding journal articles with US Food and Drug Administration (FDA) medical reviews.

Methods: We conducted a cross-sectional study of a randomly selected sample of new molecular entities approved during the study period 1 January 2013 to 31 December 2015. We extracted data on SAEs and mortality from 15 pivotal trials from ClinicalTrials.gov and corresponding journal articles (the two index resources), and FDA medical reviews (reference standard). We estimated the magnitude of deviations in rates of SAEs and mortality between the index resources and the reference standard.

Results: We found deviations in rates of SAEs (30% in ClinicalTrials.gov and 30% in corresponding journal articles) and mortality (72% in ClinicalTrials.gov and 53% in corresponding journal articles) when compared with the reference standard. The intra-class correlation coefficient between the three resources was 0.99 (95% confidence interval [CI] 0.98–0.99) for SAE rates and 0.99 (95% CI 0.97–0.99) for mortality rates.

Conclusion: There are differences in data on rates of SAEs and mortality in randomized clinical trials in both ClinicalTrials.gov and journal articles compared with FDA reviews. Further efforts should focus on decreasing existing discrepancies to enhance the transparency and reproducibility of data reporting in clinical trials.

Vitamin B6 in Health Supplements and Neuropathy: Case Series Assessment of Spontaneously Reported Cases

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ABSTRACT

Introduction: In the literature, vitamin B6 has been linked to the development of polyneuropathy. Most often, these complaints were seen when taking high doses of vitamin B6 for a long time. Evidence as to whether a lower dosage range of vitamin B6 (< 50 mg/day) can also induce neuropathy is scarce.

Objective: We aim to comprehensively describe the cases of neuropathy associated with vitamin B6 received by the Netherlands Pharmacovigilance Centre Lareb and to assess the case series concerning the use of vitamin B6 and neuropathic complaints.

Methods: We describe the number and nature of the reported cases, including suspect product, dosage, duration of use, and vitamin B6 serum levels. In addition, we describe the causality for the individual cases (Naranjo Probability Scale) and for the entire case series (Bradford Hill criteria).

Results: In total, 90 reports on products containing vitamin B6 included at least one adverse drug reaction in the standardized Medical Dictionary for Regulatory Activities (MedDRA®) query (SMQ; broad) 'peripheral neuropathy'. The amount of vitamin B6 in the products varied between 1.4 and 100 mg per tablet. The serum vitamin B6 level was known in 36 cases (88–4338 nmol/l), and the mean serum vitamin B6 level was 907 nmol/l. However, no statistical correlation between dosage and vitamin B6 blood levels was found.

Discussion and Conclusion: Causality assessment of the case series of 90 reports to Lareb shows it is plausible for the vitamin B6 supplements to have caused complaints such as neuropathies. This is especially the case with higher dosages and prolonged use, but dosages < 50 mg/day also cannot be excluded.

Safety Experience during Real-World Use of Injectable Artesunate in Public Health Facilities in Ghana and Uganda: Outcomes of a Modified Cohort Event Monitoring Study (CEMISA)

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ABSTRACT

Introduction: Injectable artesunate (Inj AS) is the World Health Organization (WHO)-recommended product for treating severe malaria. However, despite widespread usage, there are few published safety studies involving large populations in real-world settings. In this study, we sought to assess the incidence of common adverse events (AEs) following the intake of Inj AS in real-life settings.

Methods: This is a modified cohort event monitoring study involving patients who were administered with Inj AS at eight sites (four each in Ghana and Uganda) between May and December 2016. Patients were eligible for inclusion if they had severe/complicated malaria and were able and willing to participate in the study. Eligible patients were followed up by telephone or hospital or home visit on Days 7, 14, 21 and 28 after drug administration to document AEs and serious AEs (SAEs). Patients were also encouraged to report all AEs at any time during the study period. The Kaplan–Meier method was used to estimate the proportion of patients with any AEs by end of Day 28. Causality assessment was made on all AEs/SAEs using the WHO/UMC (Uppsala Monitoring Centre) causality method.

Results: A total of 1103 eligible patients were administered Inj AS, of which 360 patients were in Ghana and 743 in Uganda. The incidence of any AE by the end of follow-up among patients treated with AS was estimated to be 17.9% (197/1103) (95% confidence interval [CI] 15.8–20.3). The median time-to-onset of any AEs was 9 days (interquartile range (IQR) = 4, 14). The top five AEs recorded among patients treated with AS were pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%). Most of these top five AEs occurred in the first 14 days following treatment. Regarding the relatedness of these AEs to Inj AS, 78.9% of pyrexia (30/38), 63.0% of pain (17/27), 68.4% of diarrhoea (13/19), 85.5% of cough (14/16) and 75.0% of asthenia (12/16) were assessed as 'possibly' related. There were 17 SAEs including 13 deaths. Two of the deaths are 'possibly' related to Inj AS, as were three non-fatal SAEs: severe abdominal pain, failure of therapy and severe anaemia.

Conclusion: The incidence of common AEs among patients treated with Inj AS in real-world settings was found to be relatively low. Future studies should consider larger cohorts to document rare AEs as well.

Exploring the Potential Routine Use of Electronic Healthcare Record Data to Strengthen Early Signal Assessment in UK Medicines Regulation: Proof-of-Concept Study

Katherine Donegan, Rebecca OwenHelena BirdBrian BurchAlex SmithPhil Tregunno

ABSTRACT

Introduction: Electronic healthcare record (EHR) databases are used within pharmacoepidemiology studies to confirm or refute safety signals arising from spontaneous adverse event reports. However, there has been limited routine use of such data earlier in the signal management process, to help rapidly contextualise signals and strengthen preliminary assessment or to inform decisions regarding action including the need for further studies. This study explores the value of EHR used in this way within a regulatory environment via an automated analysis platform.

Methods: Safety signals raised at the UK Medicines and Healthcare products Regulatory Agency (MHRA) between July 2014 and June 2015 were individually reviewed by a multi-disciplinary team. They assessed the feasibility of identifying the exposure and event of interest using primary care data from the Clinical Practice Research Datalink (CPRD) within the Commonwealth Vigilance Workbench (CVW) Longitudinal Module platform, which was designed to facilitate routine descriptive analysis of signals using EHR. Three signals, where exposure and event could be well identified, were retrospectively analysed using the platform.

Results: Of 69 unique new signals, 20 were for drugs prescribed predominately in secondary care or available without prescription, which would not be identified in primary care. A further 17 were brand, formulation, or dose-specific issues, were related to mortality, were relevant only to a subgroup of patients, or were drug interactions, and hence could not be reviewed using the platform given its limitations. Analyses of exposure and incidence of the adverse event could be produced using CPRD within the CMV Longitudinal Module for 32 (46%) signals. The case studies demonstrated that the data provided supporting evidence for confirming initial assessment of the signal and deciding upon the need for further action.

Conclusions: CPRD can routinely provide useful early insights into clinical context when assessing a large proportion of safety signals within a regulatory environment provided that a flexible approach is adopted within the analysis platform.

Non-bleeding Adverse Events with the Use of Direct Oral Anticoagulants: A Sequence Symmetry Analysis

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ABSTRACT

Introduction; Postmarketing pharmacovigilance reports have raised concerns about non-bleeding adverse events associated with direct oral anticoagulants (DOACs), but only limited results are available from large claims databases.

Objective: The aim of this study was to assess the potential association between DOAC initiation and the onset of four types of non-bleeding adverse events by sequence symmetry analysis (SSA).

Methods: SSA was performed using nationwide data from the French National Healthcare databases (Régime Général, 50 million beneficiaries) to assess a cohort of 386,081 DOAC new users for the first occurrence of four types of non-bleeding outcomes: renal, hepatic, skin outcomes identified by using hospitalization discharge diagnoses, and gastrointestinal outcomes by using medication reimbursement. Asymmetry in the distribution of each investigated outcome occurring before and after initiation of DOAC therapy was used to test the association between DOAC therapy and these outcomes. SSA inherently controls for time-constant confounders, and adjusted sequence ratios were computed after correcting for temporal trends. Negative (glaucoma) and positive (bleeding, depressive disorders) control outcomes were used and analyses were replicated on a cohort of 310,195 patients initiating a vitamin K antagonist (VKA).

Results: This study demonstrated the expected positive association between either DOAC or VKA therapy and hospitalised bleeding and initiation of antidepressant therapy, while no association was observed between either DOAC or VKA therapy and initiation of antiglaucoma medications. For DOAC therapy, signals were the associations with hepatic outcomes, including acute liver injury [for the 3-month time window, aSR3 = 2.71, 95% confidence interval (CI) 1.79–4.52]; gastrointestinal outcomes, including initiation of drugs for constipation and antiemetic drugs (aSR3 = 1.31, 95% CI 1.27–1.36; and 1.17, 95% CI 1.12–1.22, respectively); and kidney diseases (aSR3 = 1.33, 95% CI 1.29–1.37).

Conclusion: Results of this nationwide study suggest that DOACs are associated with rare but severe liver injury and more frequent gastrointestinal disorders. A low risk of kidney injury with DOAC therapy can also not be excluded.

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Challenges and Opportunities for the Traceability of (Biological) Medicinal Products

Kevin Klein, Pieter Stolk

ABSTRACT

This article provides an overview of the current situation regarding the traceability of medicinal products, with a focus on drug safety and biologics. Limited traceability of biologics, in particular with regard to the batch number, is associated with incomplete recording of exposure information in clinical practice. The current pharmaceutical barcode standards in the EU do not support the automatic recording of dynamic product information, such as batch numbers and expiry dates, by means of electronic barcode scanning in clinical practice. New barcode requirements, such as the 2D DataMatrix with encoded batch numbers and expiry dates, provided on both the primary and the secondary package, can facilitate routine barcode scanning at all points in the supply chain in different healthcare settings. To build a full track-and-trace system for medicines with electronic capture of relevant exposure information, alignment with other topics, such as the Falsified Medicines Directive and initiatives to reduce medication errors, is needed to increase the buy-in from all stakeholders and to solve multiple issues with a joint effort.

Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature

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ABSTRACT

Introduction: Chloroquine and hydroxychloroquine are widely used in the long-term treatment of connective tissue disease and usually considered safe. However, chloroquine- or hydroxychloroquine-related cardiac disorder is a rare but severe adverse event, which can lead to death. This systematic review investigates cardiac complications attributed to chloroquine and hydroxychloroquine.

Methods: PubMED, EMBASE, and Cochrane database searches were conducted using keywords derived from MeSH terms. Reports published prior to 31 July, 2017 were eligible for inclusion, without restriction to study design. Searches were also conducted on reference lists of included studies.

Results: Eighty-six articles were identified, reporting individual cases or short series, providing information on 127 patients (65.4% female). A majority of patients were treated with chloroquine (58.3%), with the remaining treated with hydroxychloroquine (39.4%), or both in succession. Most patients had been treated for a long time (median 7 years, minimum 3 days; maximum 35 years) and with a high cumulative dose (median 1235 g for hydroxychloroquine and 803 g for chloroquine). Conduction disorders were the main side effect reported, affecting 85% of patients. Other non-specific adverse cardiac events included ventricular hypertrophy (22%), hypokinesia (9.4%), heart failure (26.8%), pulmonary arterial hypertension (3.9%), and valvular dysfunction (7.1%). For 78 patients reported to have been withdrawn from treatment, some recovered normal heart function (44.9%), while for others progression was unfavorable, resulting in irreversible damage (12.9%) or death (30.8%).

Limitations: The risk of cardiac complications attributed to chloroquine/hydroxychloroquine was not quantified because of the lack of randomized controlled trials and observational studies investigating the association.

Conclusions: Clinicians should be warned that chloroquine- or hydroxychloroquine-related cardiac manifestations, even conduction disorders without repercussion, may be initial manifestations of toxicity, and are potentially irreversible. Therefore, treatment withdrawal is required when cardiac manifestations are present.

Inadequate harms reporting in randomized control trials of antibiotics for pediatric acute otitis media: a systematic review

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ABSTRACT

Introduction: Reporting of harms in randomized control trials is often inconsistent and inadequate.

Objective: To assess the quality of harms reporting in randomized control trials evaluating the efficacy of antibiotics used to treat pediatric acute otitis media and to investigate whether connections to pharmaceutical companies or the publication of the CONSORT-Harms extension influenced the quality of harms reporting.

Study design and setting: We considered randomized control trials that evaluated the efficacy and safety of antibiotic treatment for uncomplicated acute otitis media in children aged 0–19. We evaluated the quality of harms reporting using a 19-item checklist addressing the recommendations endorsed in the CONSORT-Harms extension.

Results: 160 studies met our inclusion criteria. Overall quality of reporting relating to harms was low; on average studies adhered to 55.2% of the checklist items on the quality of harms reporting. The reporting of methods relating the measurement of harms was particularly lacking; studies adhered to an average of only 33.2% of the checklist items. The overall quality of reporting did not change after the publication of the CONSORT-Harms extension. The overall quality of reporting did not differ significantly in reports with or without declared connections to pharmaceutical companies (mean quality score of 56.8% vs 52.0%, respectively).

Conclusions: Harms reporting in pediatric randomized trials, especially the reporting of methods used to collect harms data, remains inadequate.

Association of Statin Use with Increased Risk of Musculoskeletal Conditions: A Retrospective Cohort Study

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ABSTRACT

Introduction: Musculoskeletal conditions, including osteoarthritis (OA), result in tremendous disability and cost. Statins are among the most commonly prescribed medications and their use for primary prevention in many otherwise healthy individuals, including those who are physically active, is increasing. There is conflicting evidence regarding the relationship of statin use and musculoskeletal conditions. Given the rising disability associated with musculoskeletal conditions, understanding predisposing factors, including medication-related exposures, deserves further attention.

Objectives: We examined the association between statin use and the risk of being diagnosed with non-traumatic arthropathies, use-related injury, and undergoing rehabilitation in a cohort with longitudinal follow-up.

Methods: Patients enrolled in a regional military healthcare system between 2003 and 2012 were evaluated in this retrospective cohort study. A propensity score was generated to match statin-users and nonusers using 115 baseline characteristics. Outcomes included ICD-9 diagnoses codes for Agency for Healthcare Research and Quality disease categories of: non-traumatic arthropathies, use-related injury and undergoing rehabilitation. Primary analysis examined the outcomes in statin-users and nonusers after propensity score matching using conditional logistic regression analysis.

Results: Initially, 60,455 patients were identified. We propensity score-matched 6728 statin users with 6728 nonusers (52 years of age, ~ 47% women). In the propensity score-matched cohort, non-traumatic arthropathies occurred in 59.8% of statin users and 56.0% of nonusers [odds ratio (OR) 1.17, 95% confidence interval (95% CI) 1.09–1.25] and use related injury occurred in 31.9% of statin users and 29.8% of nonusers (OR 1.11, 95% CI 1.03–1.19). There was no difference between statin users and nonusers undergoing rehabilitation (22.6% among statin users, 21.9% among nonusers, OR 1.04, 95% CI 0.96–1.13).

Conclusion: Statin use was associated with a significant increased risk of non-traumatic arthropathies and use-related injury. Our results provide additional data that can inform patient and clinician conversations about the benefits and risks of statin use.

Cohort Study of Psychiatric Adverse Events Following Exposure to Levonorgestrel-Containing Intrauterine Devices in UK General Practice

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ABSTRACT

Introduction: Intrauterine devices are implantable contraceptives of which some brands steadily release levonorgestrel over an extended time period. Exposure to a levonorgestrel-releasing intrauterine device has been associated with depression and, more recently, a connection to anxiety, panic attacks, sleep problems and restlessness has been suggested. This study uses data from the THIN database of UK general practice to investigate these suggestions.

Methods: A cohort study was performed to compare the incidence of psychiatric adverse events between groups of women who were new users of levonorgestrel-releasing and non-hormonal intrauterine devices. Hazard ratios for the first occurrence of psychiatric symptoms or prescriptions of disease-specific treatments were calculated on an intention-to-treat basis using a proportional hazards model.

Results: Significant associations were found between levonorgestrel exposure and records of anxiety (hazard ratio = 1.18; 95% confidence interval 1.08–1.29) and sleep problems (hazard ratio = 1.22; 95% confidence interval 1.08–1.38) in women without a prior record of these events. No significant associations were found for panic attacks or restlessness. Clear baseline differences in clinical characteristics and age between the groups were present. These were included in the model as potential confounding factors.

Conclusion: Statistically significant associations of levonorgestrel exposure with anxiety and sleep problems were observed. Substantive differences in baseline characteristics of the treated groups make robust conclusions difficult but the results strongly suggest that additional studies are warranted.

Potentially Inappropriate Medication Prescribing and Risk of Unplanned Hospitalization among the Elderly: A Self-Matched, Case-Crossover Study

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ABSTRACT

Introduction/Objectives: An association between potentially inappropriate medication (PIM) use and adverse events has been established. However, PIM criteria for elderly patients and medical circumstance vary in different countries. We investigated the association between PIM use according to Japanese guidelines and unplanned hospitalization among elderly patients.

Design: A case-crossover study was conducted.

Setting/Participants: We used the Japanese Medical Data Vision database of 17.9 million people from 270 acute care hospitals across Japan. Records from 247,897 patients aged ≥ 65 years with unscheduled admissions between January 2009 and December 2015 were analyzed.

Measurements: We defined PIM use according to the Japanese Guidelines for Medical Treatment and Its Safety in the Elderly and used conditional logistic regression analysis to fit self-matched case-crossover models and compared each patient's PIM use over five case periods (1, 2, 4, 8, and 12 weeks) prior to each unplanned hospitalization.

Results: We found the highest odds ratios (ORs) of unscheduled admission related to PIM use in the 1-week case period [OR 4.15; 95% confidence interval (CI) 4.05–4.25], followed by the 2-week (OR 3.01; 95% CI 2.95–3.07), 4-week (OR 3.91; 95% CI 3.83–4.00), 8-week (OR 2.00; 95% CI 1.96–2.05), and 12-week case periods (OR 1.48; 95% CI 1.44–1.51).

Conclusions: Elderly patients commonly used PIMs, especially antidiabetics and diuretics. PIM use was associated with a 1.5- to 4-fold increase in the ORs of unplanned hospitalization among them.

Characteristics, Quality and Contribution to Signal Detection of Spontaneous Reports of Adverse Drug Reactions via the WEB-RADR Mobile Application: A Descriptive Cross-Sectional Study

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ABSTRACT

Introduction: Spontaneous reporting of suspected adverse drug reactions is key for efficient post-marketing safety surveillance. To increase usability and accessibility of reporting tools, the Web-Recognising Adverse Drug Reactions (WEB-RADR) consortium developed a smartphone application (app) based on a simplified reporting form.

Objective: The objective of this study was to evaluate the characteristics, quality and contribution to signals of reports submitted via the WEB-RADR app.

Methods: The app was launched in the UK, the Netherlands and Croatia between July 2015 and May 2016. Spontaneous reports submitted until September 2016 with a single reporter were included. For each country, app reports and reports received through conventional means in the same time period were compared to identify characteristic features. A random subset of reports was assessed for clinical quality and completeness. The contribution to signal detection was assessed by a descriptive analysis.

Results: Higher proportions of app reports were submitted by patients in the UK (28 vs. 18%) and Croatia (32 vs. 7%); both $p < 0.01$. In the Netherlands, the difference was small (60 vs. 57%; $p = 0.5$). The proportion of female patients and the median patient ages in app reports submitted by patients were similar to the reference. The proportion of reports of at least moderate quality was high in both samples (app: 78–85%, reference: 78–98%), for all countries. App reports contributed to detecting eight potential safety signals at the national level, four of which were eventually signalled.

Conclusion: The WEB-RADR app offers a new route of spontaneous reporting that shows promise in attracting reports from patients and that could become an important tool in the future. Patient demographics are similar to conventional routes, report quality is sufficient despite a simplified reporting form, and app reports show potential in contributing to signal detection.

Potential Risk Window for Opioid Overdose Related to Treatment with Extended-Release Injectable Naltrexone

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ABSTRACT

Extended-release (ER) injectable naltrexone (Vivitrol®) is a monthly injection approved for the treatment of opioid use disorder in the US. Other treatments for opioid use disorder include opioid agonists or partial agonists such as methadone and buprenorphine-containing products (e.g. buprenorphine-naloxone). As an opioid antagonist, naltrexone blocks the euphoric effects of opioids and may reduce the risk of opioid overdose once individuals are successfully induced into treatment [1]. However, paradoxically, the risk of opioid overdose may increase if individuals try to challenge the opioid blockade associated with naltrexone [2]. Two recent studies raise concerns about the susceptibility to opioid overdose associated with ER injectable naltrexone. In a randomized trial (n =570) comparing the effectiveness of buprenorphine-naloxone with ER injectable naltrexone, 15 individuals had 18 overdose events in the ER injectable naltrexone arm, compared with 8 individuals who had 10 overdose.

Review of Case Narratives from Fatal Overdoses Associated with Injectable Naltrexone for Opioid Dependence

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ABSTRACT

Introduction: An extended-release injectable naltrexone suspension (Vivitrol®) was approved in USA in 2010 for the prevention of relapse to opioid dependence. Concerns, raised at the time of approval, about rebound overdose risk following the last dose, have not been adequately studied. We sought to determine the time period of concern for fatal overdose associated with Vivitrol.

Methods: We performed a retrospective case review of Vivitrol spontaneous reports (October 2010–March 2016) in the US Food and Drug Administration Adverse Event Reporting System via the Freedom of Information Act. Case narratives were manually reviewed to identify overdose deaths amongst current and former patients, extracting information on the time from discontinuation, followed by causality assessment.

Results: Narratives on 263 deaths and overdose-related outcomes were obtained. One hundred and forty-five death reports were assessed for causality. Among these reports, cause of death was unknown in 46%, while 52 fatal overdoses met the case definition. Of 52 overdoses, time between the last dose and death was known for 28; 22 (84.6%) occurred within 2 months of the last Vivitrol injection [median 46 days (interquartile range 29.5–82)]. The sponsor's causality assessment in 75% of fatal overdoses repeated verbatim text that placed responsibility on underlying opioid dependence and precluded a link between medication and overdose or ignored rebound risk following treatment discontinuation.

Conclusions: Vivitrol adverse event reports suggest the need to investigate two months following the last medicine injection as a period of particular concern for overdose. A registry study would best quantify risk. Providers should report suspected post-discontinuation overdoses to government authorities.

What Future Healthcare Professionals Need to Know About Pharmacovigilance: Introduction of the WHO PV Core Curriculum for University Teaching with Focus on Clinical Aspects

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ABSTRACT

Adverse drug reactions (ADRs) can cause serious health problems, as shown in studies about drug-related hospitalizations. To build knowledge of and raise awareness about ADRs among healthcare professionals, more education in the field of ADRs and pharmacovigilance (PV) is needed. No standard exists for teaching PV at universities for medical, pharmacy, dentistry and nursing students, so a core curriculum needs to be developed to teach important aspects of PV to students. In September 2016, a stakeholders' meeting was initiated on behalf of the World Health Organization (WHO) and organized by the Netherlands Pharmacovigilance Centre Lareb. This meeting addressed and agreed on the PV competencies students need to develop and what key aspects of the subject should be taught. Five key aspects were identified: understanding the importance of PV in the context of pharmacotherapy, and preventing, recognizing, managing and reporting ADRs. Since time and resources for PV education are limited, elements of the WHO PV core curriculum for university teaching were designed to be integrated into existing courses but can be used as a stand-alone programme. The basis of and outline for the WHO PV core curriculum for university teaching are addressed in this paper. It is expected that PV competencies for students are vital for their contribution to safe use of medicines in the future. In addition, this article aims to stimulate discussion on this subject and promote collaboration between universities, national PV centres and other stakeholders to integrate key aspects of PV in their educational programmes.

Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction

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ABSTRACT

In recent years, marketing of highly innovative and costly biologics improved the management of high-burden diseases such as autoimmune diseases, cancers, and chronic renal failure. Several widely prescribed biologics have recently lost or will shortly lose their patents, thus opening avenues to the marketing of a growing number of biosimilars worldwide, which are products similar in terms of quality, safety, and efficacy to already licensed reference products, thus allowing for potential savings in pharmaceutical expenditure. Numerous debates about the interchangeability between biosimilars and reference products are still ongoing, owing to concerns about potential immunogenicity raised by switching, which may cause a lack of effect and toxicity. Patients successfully treated with biologic therapy may theoretically receive biosimilars to contain costs, if reference product and related biosimilar are judged as interchangeable. However, the positions of regulatory agencies on the interchangeability and automatic substitution of biologics with biosimilars are very different. The benefit-risk profile of biosimilars has been often questioned by clinicians owing to the limited amount of pre-marketing information on clinical efficacy and safety, despite biosimilarity being based on a comparability exercise with the reference product to gain the biosimilar approval. Nevertheless, after more than 10 years of marketing from the first biosimilar approval in Europe, no proof of differences in terms of the safety profile of biosimilars and originators has been reported. In this context, post-marketing evaluation of both biologics and biosimilars safety profiles through analyses from spontaneous reporting databases and claims databases is crucial. An important issue for the pharmacovigilance of biologics concerns the traceability, indicating the brand name and batch number in spontaneous adverse drug reaction reports, but this requirement is not frequently addressed. This review aims to provide an overview of the characteristics and potential challenges in the safety profile assessment of biologics with a focus on the post-marketing setting.

Prescription Opioid Fatalities: Examining Why the Healer could be the Culprit

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ABSTRACT

Prescription opioid use has increased rapidly in developed countries, as have fatalities and other related adverse events. This review examines the intrinsic characteristics of opioids, including their mechanisms of action and pharmacokinetic and pharmacodynamic properties, to determine how the use of a regonised pharmacological remedy for a medically confirmed ailment could result in an accidental fatality. Opioids trigger biological processes that inhibit their own therapeutic effect. Prolonged use of opioids can result in activation of pronociceptive systems, leading to opioid-induced hyperalgesia and tolerance, while opioid metabolites can antagonise the antinociceptive action of the parent drug, also leading to opioid-induced hyperalgesia and tolerance. Pain stimulates respiration and counteracts the respiratory depression effect of opioids. Analgesia from opioids leads to loss of this protective mechanism, leading to increased risk of death due to respiratory failure. Increased patient counseling during opioid prescribing and dispensing, and limiting prescription to short-term use in non-malignant pain, may decrease the adverse effects of opioids. The vast majority of patients who unintentionally experience serious adverse events from pharmaceutical opioids do not start out as drug seekers. Even opioid use within prescribing guidelines can place some patients at risk of death and may prevent patients from seeking help for prescription opioid dependence.

Safety Profile of Benznidazole in the Treatment of Chronic Chagas Disease: Experience of a Referral Centre and Systematic Literature Review with Meta-Analysis

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ABSTRACT

Introduction: Benznidazole is the preferred drug for treatment of Chagas disease. However, it is toxic and of limited value in chronic infection.

Objective: We aimed to estimate the rates of and factors related to adverse reactions (ARs) to benznidazole and treatment discontinuations (TDs).

Methods: A meta-analysis was performed using an electronic search of the published literature with no language restrictions until June 2017. Prospective studies were included of chronically infected patients in which at least one treatment arm included benznidazole. Data were added from a prospective cohort of patients with Chagas disease at our centre (January 2007–June 2017). Weighted rates of ARs and TDs were estimated, and potentially related factors were analysed.

Results: Some 413 studies were found, from which we chose 42 (nine clinical trials and 33 observational studies, including ours), comprising data for 7822 patients. The weighted rate of ARs to benznidazole was 44.1% (95% confidence interval [CI] 37.2–51.2). ARs were more frequent in adults than in children (51.6 vs. 24.5%), with the most common being skin reactions (34%), gastrointestinal complaints (12.6%) and neurological symptoms (11.5%). Grade 4 ARs were recorded in 3% of cases. The weighted rate of TDs was 11.4% (95% CI 8.5–14.5); TDs were more frequent in adults than in children (14.2 vs. 3.8%). In our cohort, only female sex was related to an increased rate of ARs but not to TDs.

Conclusion: Benznidazole had a poor tolerability profile, with a high incidence of TDs, especially in adult patients and women. Optimised dosing schedules and/or new drugs are urgently needed.

Coronary Events after Dispensing of Ibuprofen: A Propensity Score-Matched Cohort Study versus Paracetamol in the French Nationwide Claims Database Sample

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ABSTRACT

Introduction: Non-steroidal anti-inflammatory drugs are associated with a dose and duration-dependent coronary risk. There is little information concerning analgesic-dose ibuprofen, among the most widely used drugs worldwide.

Objective: Our objective was to measure the risks of acute coronary syndrome (ACS) after dispensing of ibuprofen, versus paracetamol.

Methods: Propensity score 1:2-matched cohorts of ibuprofen or paracetamol treatment episodes (TEs) in Echantillon Généraliste de Bénéficiaires (EGB), the 1/97 sample of Système National des Données de Santé (SNDS), the French nationwide claims database, from 2009 to 2014, were compared. Outcomes were hospital admissions for ACS during the 3 months after the dispensing of ibuprofen or paracetamol. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated overall and stratified on low-dose aspirin dispensing.

Results: A total of 315,269 ibuprofen TEs in 168,400 persons were matched to 630,457 paracetamol TEs in 395,952 patients. Event rates were 50–100 times higher in low-dose aspirin users (27 vs 0.28 per 1000 patient years). Overall there was no difference in risk of ACS at 3 months (HR 0.94, 95% CI 0.74–1.20) despite a transient increase in the first 2 weeks in ibuprofen users (HR 1.70, 95% CI 1.11–2.59). In the stratified analysis, this short-term risk was only found in aspirin users (5% of population, HR 1.84, 95% CI 1.24–3.24), but not in non-aspirin users (HR 1.09, 95% CI 0.40–2.94).

Conclusions: There was no evidence for an increased risk of ACS in patients dispensed ibuprofen compared to paracetamol.

Predicting Adverse Drug Effects from Literature- and Database-Mined Assertions

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ABSTRACT

Introduction: Given that adverse drug effects (ADEs) have led to post-market patient harm and subsequent drug withdrawal, failure of candidate agents in the drug development process, and other negative outcomes, it is essential to attempt to forecast ADEs and other relevant drug–target–effect relationships as early as possible. Current pharmacologic data sources, providing multiple complementary perspectives on the drug–target–effect paradigm, can be integrated to facilitate the inference of relationships between these entities.

Objective: This study aims to identify both existing and unknown relationships between chemicals (C), protein targets (T), and ADEs (E) based on evidence in the literature.

Materials and Methods: Cheminformatics and data mining approaches were employed to integrate and analyze publicly available clinical pharmacology data and literature assertions interrelating drugs, targets, and ADEs. Based on these assertions, a C–T–E relationship knowledge base was developed. Known pairwise relationships between chemicals, targets, and ADEs were collected from several pharmacological and biomedical data sources. These relationships were curated and integrated according to Swanson's paradigm to form C–T–E triangles. Missing C–E edges were then inferred as C–E relationships.

Results: Unreported associations between drugs, targets, and ADEs were inferred, and inferences were prioritized as testable hypotheses. Several C–E inferences, including testosterone → myocardial infarction, were identified using inferences based on the literature sources published prior to confirmatory case reports. Timestamping approaches confirmed the predictive ability of this inference strategy on a larger scale.

Conclusions: The presented workflow, based on free-access databases and an association-based inference scheme, provided novel C–E relationships that have been validated post hoc in case reports. With refinement of prioritization schemes for the generated C–E inferences, this workflow may provide an effective computational method for the early detection of potential drug candidate ADEs that can be followed by targeted experimental investigations.

MOdified NARanjo Causality Scale for ICSRs (MONARCSi): A Decision Support Tool for Safety Scientists

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ABSTRACT

Introduction: Within the field of Pharmacovigilance, the most common approaches for assessing causality between a report of a drug and a corresponding adverse event are clinical judgment, probabilistic methods and algorithms. Although multiple methods using these three approaches have been proposed, there is currently no universally accepted method for assessing drug-event causality in ICSRs and variability in drug-event causality assessments is well documented.

Objective: This study describes the development and validation of an Individual Case Safety Report (ICSR) Causality Decision Support Tool to assist Safety Professionals (SPs) performing causality assessments.

Methods: Roche developed this model with nine drug-event pair features capturing important aspects of Naranjo's scoring system, selected Bradford–Hill criteria, and internal Roche safety practices. Each of the features was weighted based on individual safety professional (n = 65) assessments of the importance of that feature when assessing causality, using an ordinal weighting scale (0 = no importance, 4 = very high importance). The mean and associated standard deviation for each feature weight was calculated and were used as inputs to a fitted logistic equation, which calculated the probability of a causal relationship between the drug and adverse event. Model training, validation, and testing were conducted by comparing MONARCSi causality classifications to previous company causality assessments for 978 randomly selected, clinical trial drug-event pairs based on their respective features and weights.

Results: The final model test, a two-by-two comparison of the results, showed substantial agreement (Gwet Kappa = 0.77) between MONARCSi and Roche safety professionals' assessments of causality, using global introspection. The model exhibited moderate sensitivity (65%) and high specificity (93%), high positive and negative predictive values (79 and 88%, respectively), and an F1 score of 71%.

Conclusion: Analysis suggests that the MONARCSi model could potentially be a useful decision support tool to assist pharmacovigilance safety professionals when evaluating drug-event causality in a consistent and documentable manner.

Role of Serotonin Transporter in Antidepressant-Induced Diabetes Mellitus: A Pharmacoepidemiological–Pharmacodynamic Study in VigiBase®

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ABSTRACT

Background: The association between antidepressant exposure and type 2 diabetes mellitus is still debated. Moreover, the pharmacological mechanisms remain unknown.

Objective: The objective of this study was to investigate this putative relationship with the role of antidepressant pharmacological targets using the 'pharmacoepidemiological–pharmacodynamic' method.

Methods: First, we performed case/non-case analyses in VigiBase® (the World Health Organization international database of suspected adverse drug reactions) to examine a signal of increased type 2 diabetes reporting (expressed as the reporting odds ratio and its 95% confidence interval) for antidepressants in general; examine and rank type 2 diabetes signals between the different pharmacological classes of antidepressants and the different antidepressants (58 in total). Second, we performed linear regression analyses to explore the association between the type 2 diabetes signal ranked between antidepressants and their binding affinities for nine targets (serotonin, norepinephrine, dopamine transporters, 5-HT2C serotonin, D2 dopamine, α1, α2 adrenergic, M3 muscarinic and H1 histamine receptors).

Results: A significant type 2 diabetes signal was found for antidepressants in general, three classes of antidepressants (tricyclic antidepressants, serotonin reuptake inhibitors and "other" antidepressants) and 15 individual antidepressants in particular. Among the antidepressants, three serotonin reuptake inhibitors [escitalopram (adjusted reporting odds ratio 1.15 [1.07–1.25]), paroxetine (1.15 [1.07–1.23]), sertraline (1.23 [1.17–1.31])] and three "other" antidepressants [duloxetine (1.15 [1.07–1.23]), trazodone (1.20 [1.09–1.32]), venlafaxine (1.15 [1.08–1.23])] were the antidepressants most frequently reported with type 2 diabetes. We found a significant correlation between the type 2 diabetes signal and serotonin transporter affinity (slope = 0.14 [0.06–0.23], $p = 0.003$, $R2 = 0.43$) but not the other targets.

Conclusion: The present study suggests a potential role for serotonin transporter in antidepressant-induced type 2 diabetes.

First Conference on Big Data for Pharmacovigilance

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ABSTRACT

Introduction: With the increasing availability of data in medicine and healthcare, the term 'big data' has undoubtedly become one of the biggest buzzwords in biomedical research in recent years. It has been associated with other hot topics such as machine learning and artificial intelligence and is beginning to revolutionize pharmacoepidemiology and pharmacovigilance. Big data refer to data of large size (volume) that evolve quickly (velocity), contain heterogeneous sets of information (variety), and encompass data of varying quality (veracity) [1]. Although big data are not new, digitization of clinical and health-related data that were previously managed in hard copy format is changing the research landscape [2]. Real-world data (RWD) are information routinely collected as part of patient care, such as electronic health records (EHRs), administrative claims data, images and readings from medical equipment, and laboratory results. Other sources to ascertain patients' health status and.

Enhancing Pharmacovigilance Capabilities in the EU Regulatory Network: The SCOPE Joint Action

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ABSTRACT

In November 2013, a team of European regulators initiated the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. Funded by the Health Programme of the European Union, and with contributions from the involved Member States, SCOPE gathered information and expertise on how regulators in Member States run their national pharmacovigilance systems to meet the requirements of the pharmacovigilance legislation that came into effect in June 2012. The SCOPE project evaluated then-current practices and developed tools to further improve the skills and capability in the pharmacovigilance network. The project was divided into eight separate work streams, five of which concentrated on pharmacovigilance topics—collecting information on suspected adverse drug reactions, identifying and managing safety issues (signals), communicating risk and assessing risk minimisation measures, supported by effective quality management systems. The other three work streams focused on the functional aspects—coordination, communication and evaluation of the project. Through the project, SCOPE delivered guidance, training in key aspects of pharmacovigilance, and tools and templates to support best practice. The deliverables provide practical guidance that those working in the European national competent authorities can take to strengthen their national systems. The SCOPE outputs can be useful for other stakeholders involved in pharmacovigilance activities, including the pharmaceutical industry, healthcare professionals, patient and consumer organisations, and academia.

Risks of Opioids in ST-Elevation Myocardial Infarction: A Review

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ABSTRACT

Although opioids are recommended and frequently used in the acute phase of ST-elevation myocardial infarction (STEMI), their use is accompanied by serious side effects. In particular, gastrointestinal adverse effects may disturb absorption of essential oral medication like platelet inhibitors. This may cause suboptimal platelet inhibition and increased risk of acute stent thrombosis. Some clinical studies have already demonstrated these negative results. Alternative strategies to optimize platelet inhibition and pain relief in STEMI are being investigated. Clinicians should become more aware of the potential side effects of opioids in STEMI.

Real World Evidence: Time for a Switch?

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ABSTRACT

Real World Evidence (RWE) provides critical information about the performance of medicines in routine clinical practice, as actually prescribed by physicians and taken by patients. For decades, observational designs and electronic healthcare databases have been used to characterize patient populations, describe the natural history of diseases, assess postapproval safety and conduct risk management programs as part of the drug development lifecycle. These approaches have evolved in recent years due to advances in electronic data collection, data linkage, computing power, the greater availability of analytic tools and methodologies, and established best practices. The US FDA Sentinel Initiative illustrates these advances well by rapidly generating evidence (in days, not months) in large populations (more than half of the US population in some analyses) and with increased transparency [1]. These advances have made possible the potential use of these systems for outcomes other than.

Evaluation of Switching Patterns in FDA's Sentinel System: A New Tool to Assess Generic Drugs

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ABSTRACT

Introduction: Nearly 90% of drugs dispensed in the US are generic products.

Objective: The aim of this study was to develop and implement a tool for analyzing manufacturer-level drug utilization and switching patterns within the US Food and Drug Administration's Sentinel system.

Methods: A descriptive tool was designed to analyze data in the Sentinel common data model and was tested with two case studies—metoprolol extended release (ER) and lamotrigine ER—using claims data from four Sentinel data partners. We plotted initiators of each brand and generic product over time. For metoprolol ER, we evaluated rates of switching from generics around the time of manufacturing issues. For lamotrigine ER, we examined rates of switching back to the brand among those who switched from brand to generic.

Results: We identified 1,651,285 initiators of metoprolol ER products between July 2008 and September 2015. We observed a large decrease in monthly metoprolol ER initiators (from 25,465 in December 2008 to 13,128 in February 2009), corresponding to recalls by generic manufacturers. We observed simultaneous increases in utilization of the authorized generic and brand products. We identified 4266 initiators of lamotrigine ER with an epilepsy diagnosis between January 2012 and September 2015. Among those who switched from brand to generic, the cumulative incidence of switching back was close to 20% at 2 years. Switchback rates were higher for the first available generic products.

Conclusions: This developed tool was able to elucidate novel utilization and switching patterns in two case studies. Such information can be used to support surveillance of generic drugs and biosimilars.

Gabapentin and Pregabalin and Risk of Atrial Fibrillation in the Elderly: A Population-Based Cohort Study in an Electronic Prescription Database

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ABSTRACT

Introduction: Gabapentin and pregabalin are widely prescribed to elderly people, but data on their pharmacokinetics, safety, and efficacy in this population are scarce. Neurological adverse effects are common. Atrial fibrillation (AF) associated with their use has been described in several case reports and case series, but the incidence is unknown.

Objective: The aim of this study was to assess the association between exposure to gabapentin or pregabalin and AF in the elderly.

Methods: Patients ≥ 65 years of age starting treatment with either gabapentin or pregabalin between January 1 and March 31, 2015, free of cardiovascular disease, and who did not receive the alternate study medications were studied. They were compared with patients who initiated treatment with an analgesic opiate or with alprazolam or diazepam. The two primary outcome variables were a first claim of an oral anticoagulant plus an antiarrhythmic drug (OAC + AA), or of an oral anticoagulant or an antiplatelet agent plus an antiarrhythmic drug (OAC/APA + AA), in the 3 months after treatment initiation.

Results: Compared with opiate analgesics, both gabapentin and pregabalin were associated with an increased risk of initiating OAC/APA + AA. The incidence was 6 of 668 (9.0 per 1000 patients) with gabapentin, versus 12 of 3889 (3.1 per 1000) with opiates, relative risk (RR) 2.91 (95% confidence interval [CI] 1.10–7.73), and for pregabalin it was 6 of 698 (8.6 per 1000) RR 2.79 (95% CI 1.05–7.40). The comparison with alprazolam/diazepam gave similar results. The risks did not vary by age, sex, or co-treatment with NSAIDs, and they increased with dose.

Conclusion: In elderly patients free of cardiovascular disease, an association between new exposure to gabapentin or pregabalin and initiating treatment for AF was found. These results should be confirmed in other studies.

Changes in Outpatient Use of Antibiotics by Adults in the United States, 2006–2015

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ABSTRACT

Introduction: Numerous initiatives over the past decade have targeted the problem of antibiotic overuse in the US; however, the cumulative impact of such initiatives upon recent patterns of use is not known.

Objectives: The aims of this study were to (1) describe general trends in outpatient antibiotic use among adults over the period 2006–2015; and (2) identify rapid shifts in use during this time period as potential indicators for key events.

Methods: This was an observational study set in the ambulatory setting. Patients ≥ 18 years of age were selected from the Optum Clinformatics Datamart™, a commercial insurance claims database. The outcome measures of interest were prescriptions filled/1000 enrolled individuals, by year or quarter. We used linear regression to identify trends in use over multiple years, and change-point regression to identify rapid shifts in use within individual years.

Results: From 2006 to 2015, antibiotic use declined significantly, decreasing by 12% for adults younger than 65 years of age (913–807 prescriptions/1000 individuals, $p = 0.0001$) and by 5% for adults ≥ 65 years of age (991–943 prescriptions/1000 individuals, $p = 0.018$). With change-point regression, we identified a number of rapid shifts in the use of specific antibiotic classes, such as downward shifts in the use of quinolones and macrolides during the second quarter of 2008 and 2013, respectively.

Conclusions: Over the period 2006–2015 outpatient use of antibiotics decreased substantially among adults. Rapid shifts in use occurring in 2008 and 2013 may reflect the presence of key drivers of change, such as abrupt changes in access to care or perceived antibiotic safety.

Adverse Drug Reactions among Patients Initiating Second-Line Antiretroviral Therapy in South Africa

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ABSTRACT

Introduction: Understanding the occurrence of antiretroviral (ARV)-related adverse events (AEs) among patients receiving second-line antiretroviral therapy (ART) is important in preventing switches to more limited and expensive third-line regimens.

Objective: This study aimed to estimate the rates and examine predictors of AEs among adult HIV-1-infected patients receiving second-line ART in the Right to Care (RTC) clinical cohort in South Africa.

Methods: This was a cohort study of HIV-1-infected adult patients (≥ 18 years of age) initiating standard second-line ART in South Africa from 1 April 2004 to 10 January 2016. Our primary outcome was the development of an AE within 24 months of initiating second-line therapy. We used Kaplan–Meier survival analysis to determine AE incidence in the first 24 months of second-line ART. Predictors of AEs were modelled using a Cox proportional hazards model.

Results: A total of 7708 patients initiated second-line ART, with 44.5% developing at least one AE over the first 24 months of second-line treatment. The highest AE incidence was observed among patients receiving abacavir (ABC) + lamivudine (3TC) + ritonavir-boosted lopinavir/atazanavir (LPVr/ATVr) (52.7/100 person-years (PYs), 95% confidence interval (CI): 42.9–64.8), while patients initiated on a tenofovir (TDF) + emtricitabine (FTC)/3TC + LPVr regimen had the lowest rate of AEs (26.4/100 PYs, 95% CI: 24.9–28.3). Clinical predictors of AEs included experiencing AEs when receiving first-line ART (adjusted hazard ratio (aHR) 2.3, 95% CI: 1.9–2.8), lower CD4 cell count (0–199 vs. ≥ 350 cells/mm3; aHR 1.4, 95% CI: 1.4–1.8), and switching to second-line therapy from an ABC-base first-line regimen (ABC + 3TC + efavirenz/nevirapine [EFV/NVP] vs. TDF + 3TC/FTC + EFV/NVP; aHR 3.4, 95% CI: 1.1–11.1).

Conclusions: The rates of AEs were lowest among patients receiving a TDF-based second-line regimen. Patients with poorer health at the time of switch were at higher risk of AEs when receiving second-line ART and may require closer monitoring to improve the durability of second-line therapy.

Assessment of the Utility of Social Media for Broad-Ranging Statistical Signal Detection in Pharmacovigilance: Results from the WEB-RADR Project

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ABSTRACT

Introduction and Objective: Social media has been proposed as a possibly useful data source for pharmacovigilance signal detection. This study primarily aimed to evaluate the performance of established statistical signal detection algorithms in Twitter/Facebook for a broad range of drugs and adverse events.

Methods: Performance was assessed using a reference set by Harpaz et al., consisting of 62 US Food and Drug Administration labelling changes, and an internal WEB-RADR reference set consisting of 200 validated safety signals. In total, 75 drugs were studied. Twitter/Facebook posts were retrieved for the period March 2012 to March 2015, and drugs/events were extracted from the posts. We retrieved 4.3 million and 2.0 million posts for the WEB-RADR and Harpaz drugs, respectively. Individual case reports were extracted from VigiBase for the same period. Disproportionality algorithms based on the Information Component or the Proportional Reporting Ratio and crude post/report counting were applied in Twitter/Facebook and VigiBase. Receiver operating characteristic curves were generated, and the relative timing of alerting was analysed.

Results: Across all algorithms, the area under the receiver operating characteristic curve for Twitter/Facebook varied between 0.47 and 0.53 for the WEB-RADR reference set and between 0.48 and 0.53 for the Harpaz reference set. For VigiBase, the ranges were 0.64–0.69 and 0.55–0.67, respectively. In Twitter/Facebook, at best, 31 (16%) and four (6%) positive controls were detected prior to their index dates in the WEB-RADR and Harpaz references, respectively. In VigiBase, the corresponding numbers were 66 (33%) and 17 (27%).

Conclusions: Our results clearly suggest that broad-ranging statistical signal detection in Twitter and Facebook, using currently available methods for adverse event recognition, performs poorly and cannot be recommended at the expense of other pharmacovigilance activities.

Comment on "Assessment of the Utility of Social Media for Broad-Ranging Statistical Signal Detection in Pharmacovigilance: Results from the WEB-RADR Project"

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ABSTRACT

We read with great interest the article titled "Assessment of the Utility of Social Media for Broad-Ranging Statistical Signal Detection in Pharmacovigilance: Results from the WEB-RADR Project" by Caster et al., published online on 24 July 2018 in Drug Safety [1]. In that paper, the authors provide evidence that broad-ranging statistical signal detection on social media, such as Facebook and Twitter, is not worthwhile compared with other pharmacovigilance activities. More product–event combinations were detected in patient forum posts than in Twitter/Facebook, but detection was delayed in forums compared with VigiBase. The authors suggest that shortcomings of the adverse event recognition algorithms may partially explain poor signal detection performance, and we agree that additional efforts must be made to take into account the patient-specific terms that do not necessarily belong to the medical language. Nevertheless, these conclusions question the utility of any future.

A Critical Evaluation of Safety Signal Analysis Using Algorithmic Standardised MedDRA Queries

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ABSTRACT

Introduction: Algorithmic Standardised MedDRA® Queries (aSMQs) are increasingly used to enhance the efficiency of safety signal detection. The manner that aSMQs affect capture of potential safety cases is unclear.

Objectives: Our objective was to characterise the performance of aSMQs with respect to their potential for double counting, the likelihood of events in aSMQ positive cases being clinically related, how frequently terms are used for algorithmically positive cases, and the face validity of positive cases based on the drug inducing events. We were also interested in what effect requiring symptoms to overlap temporally would have on performance.

Methods: We reviewed adverse event (AE) datasets of New Drug Applications and Biological License Applications and compiled a database including preferred terms and corresponding SMQs, SMQ term categories, AE start day, AE duration, drug name, and Anatomical Therapeutic Chemical class. Two reviewers independently determined if the algorithm was met and, if so, whether the broad terms overlapped temporally.

Results: A total of 107 marketing applications were reviewed, including 103,928 patients and 277,430 AEs. Use of algorithms condensed the number of AEs to between 5 and 8% and the incidence to about 1.5% relative to when the SMQs are used without the algorithm. Certain aSMQs exhibited a potential for overcounting. Requiring symptoms to temporally overlap helped to eliminate irrelevant cases.

Conclusions: Our findings demonstrate that algorithmic and temporal assessment increased specificity of case retrieval, though the reduction in the number of terms or incidence seemed excessive for certain aSMQs. Evaluating the day of AE onset and duration improve specificity through identification of outlying events. Identification of drug classes known to cause the aSMQ's clinical condition provides face validity for this tool, yet detection of cases associated with novel classes may provide new understanding of these disorders. Improvements in some of the SMQ term lists may improve the performance of SMQs in general.

Proton Pump Inhibitor Use and Risk of Developing Alzheimer's Disease or Vascular Dementia: a Case–Control Analysis

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ABSTRACT

Introduction: Long-term use of proton pump inhibitors (PPIs) has been associated with an increased risk of Alzheimer's disease (AD) in observational studies. The role of exposure duration, and whether this applies to other dementia subtypes, has not been explored in these studies.

Objective: The aim was to study the association between long-term use of PPIs (or of histamine-2 receptor antagonists [H2RAs], as a negative control) and the risk of developing AD or vascular dementia (VaD).

Methods: We conducted a case–control analysis on the UK-based Clinical Practice Research Datalink (CPRD). We identified 41,029 patients aged ≥ 65 years with newly diagnosed AD or VaD between 1998 and 2015 and matched them 1:1 to dementia-free controls on age, sex, calendar time, general practice, and number of years of recorded history. We applied conditional logistic regression analyses to calculate adjusted odds ratios (aORs), with 95% confidence intervals (CIs), of developing AD or VaD in relation to previous use of PPIs or H2RAs, categorized by exposure duration.

Results: As compared to non-use, long-term PPI use (≥ 100 prescriptions) was not associated with an increased risk of developing AD (aOR 0.88, 95% CI 0.80–0.97) or VaD (aOR 1.18, 95% CI 1.04–1.33). Neither was long-term use of H2RAs (≥ 20 prescriptions) associated with an increased risk of developing AD (aOR 0.94, 95% CI 0.87–1.02) or VaD (aOR 0.99, 95% CI 0.89–1.10).

Conclusion: In this large, case-control analysis, we did not find any evidence for an increased risk of either AD or VaD related to PPI or H2RA use.

Methods to Compare Adverse Events in Twitter to FAERS, Drug Information Databases, and Systematic Reviews: Proof of Concept with Adalimumab

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ABSTRACT

Introduction: Adverse drug reactions (ADRs) are associated with significant health-related and financial burden, and multiple sources are currently utilized to actively discover them. Social media has been proposed as a potential resource for monitoring ADRs, but drug-specific analytical studies comparing social media with other sources are scarce.

Objectives: Our objective was to develop methods to compare ADRs mentioned in social media with those in traditional sources: the US FDA Adverse Event Reporting System (FAERS), drug information databases (DIDs), and systematic reviews.

Methods: A total of 10,188 tweets mentioning adalimumab collected between June 2014 and August 2016 were included. ADRs in the corpus were extracted semi-automatically and manually mapped to standardized concepts in the Unified Medical Language System. ADRs were grouped into 16 biologic categories for comparisons. Frequencies, relative frequencies, disproportionality analyses, and rank ordering were used as metrics.

Results: There was moderate agreement between ADRs in social media and traditional sources. "Local and injection site reactions" was the top ADR in Twitter, DIDs, and systematic reviews by frequency, ranked frequency, and index ranking. The next highest ADR in Twitter—fatigue—ranked fifth and seventh in FAERS and DIDs.

Conclusion: Social media posts often express mild and symptomatic ADRs, but rates are measured differently in scientific sources. ADRs in FAERS are reported as absolute numbers, in DIDs as percentages, and in systematic reviews as percentages, risk ratios, or other metrics, which makes comparisons challenging; however, overlap is substantial. Social media analysis facilitates open-ended investigation of patient perspectives and may reveal concepts (e.g. anxiety) not available in traditional sources.

End

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