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Reversal Strategies for NOACs: State of Development, Possible Clinical Applications and Future Perspectives
Steen HustedFreek W. A. VerheugtWillemijn J. Comuth

ABSTRACT
The non-vitamin K antagonist oral anticoagulants (NOACs) are used for thromboembolic prophylaxis of patients with atrial fibrillation and in the treatment as well as secondary prophylaxis of patients with venous thromboembolism. Even though NOACs have a better safety profile than vitamin K antagonists (VKAs), there will still be bleeding complications on NOAC treatment. In some cases, stopping the NOAC and non-drug-related management such as manual compression and interventional endoscopy will be sufficient to stop the bleeding. In more serious bleeding events and before acute surgery, coagulation factor concentrates or NOAC-specific antidotes could be used. Coagulation factor concentrates can be used in patients with haemophilia and to reverse the effect of VKAs but, in NOAC-treated patients, results are inconsistent and these agents could potentially have pro-thrombotic effects. Specific antidotes for NOACs are expected to be on the market soon. Phase III clinical trials with a humanized antibody fragment directed against dabigatran (idarucizumab) and recombinant, modified factor Xa (andexanet alfa) are ongoing. A molecule (aripazine) with broad activity against various anticoagulants including NOACs is currently undergoing phase II trials. For use of these specific antidotes, it is desirable that measurements for coagulation activity with a short response delay are widely available for the different NOACs and further research in this field is needed. Furthermore, guidelines for antidote use, including general measures for the treatment of NOAC-related bleeding, should be available.

Advances in the Pharmacogenomics of Adverse Drug Reactions
Susannah L. Collins, Daniel F. Carr, Munir Pirmohamed

ABSTRACT
Rapid developments in pharmacogenomics have been noticeable in recent years, and much of this knowledge has improved understanding of adverse drug reactions. This improved knowledge has largely been the result of improved sequencing technologies and falling costs in this area, as well as improved statistical techniques to analyse the data derived from studies. While the genetic reasons behind adverse drug reactions are becoming better understood, translation of this knowledge, particularly in terms of biomarkers that might be clinically applicable at the bedside, has been more difficult. Understanding of the technologies and their application is limited among practising clinicians. The cost of some of the technologies available may also be prohibitive in stretched healthcare economies. As education about the potential for applying pharmacogenomics improves and costs fall, understanding of adverse drug reactions and application of this knowledge in a clinical setting should improve.
ABSTRACT

Introduction: Although it seems reasonable to suppose that a drug that increases the risk of an adverse event might tend to show increased disproportionality statistics in spontaneous reporting databases, that relationship is not clear. Therefore, an empirical approach was taken to investigate the relationship between proportional reporting ratios (PRRs) and relative risk (RR) estimates from formal studies in a set of known adverse drug reactions (ADRs).

Methods: Drug-event pairs that were the subject of pharmacovigilance-driven European regulatory actions from 2007 to 2010 were selected. Only pairs having RR derived from formal studies and where it was considered that there was well-established evidence supporting the actions were included. A best estimate of the RR for each ADR was chosen based on pre-specified rules. PRRs were then calculated in Eudravigilance using only those cases reported before the date of first recognition of the ADR in the medical community.

Results: From an initial dataset of 78 drug-event pairs, 15 were selected. The regression model (ln RR = 0.203 + 0.463 × ln PRR) showed a significant (p < 0.001) correlation between RR and PRR in Eudravigilance. None of the ADR-related variables analysed modified the relationship. Exploratory results in FEDRA went in the same direction.

Conclusions: Disproportionality measures should not replace formal studies but could provide an initial indication of the likely clinical importance of an ADR, should the signal be confirmed subsequently. Whether the same conclusions can be applied to other datasets should be further studied.

Feasibility of Prioritizing Drug–Drug-Event Associations Found in Electronic Health Records

Juan M. Banda, Alison Callahan, Rainer Winnenburg, Howard R. Strasberg

ABSTRACT

Background and Objective: Several studies have demonstrated the ability to detect adverse events potentially related to multiple drug exposure via data mining. However, the number of putative associations produced by such computational approaches is typically large, making experimental validation difficult. We theorized that those potential associations for which there is evidence from multiple complementary sources are more likely to be true, and explored this idea using a published database of drug–drug-adverse event associations derived from electronic health records (EHRs).

Methods: We prioritized drug–drug-event associations derived from EHRs using four sources of information: (1) public databases, (2) sources of spontaneous reports, (3) literature, and (4) non-EHR drug–drug interaction (DDI) prediction methods. After pre-filtering the associations by removing those found in public databases, we devised a ranking for associations based on the support from the remaining sources, and evaluated the results of this rank-based prioritization.

Results: We collected information for 5983 putative EHR-derived drug–drug-event associations involving 345 drugs and ten adverse events from four data sources and four prediction methods. Only seven drug–drug-event associations (<0.5 %) had support from the majority of evidence sources, and about one third (1777) had support from at least one of the evidence sources.

Conclusions: Our proof-of-concept method for scoring putative drug–drug-event associations from EHRs offers a systematic and reproducible way of prioritizing associations for further study. Our findings also quantify the agreement (or lack thereof) among complementary sources of evidence for drug–drug-event associations and highlight the challenges of developing a robust approach for prioritizing signals of these associations.
The Contribution of National Spontaneous Reporting Systems to Detect Signals of Torsadogenicity: Issues Emerging from the ARITMO Project

Emanuel Raschi, Elisabetta Poluzzi, Francesco Salvo, Ariola Koci

**ABSTRACT**

**Introduction:** Spontaneous reporting systems (SRSs) are pivotal for signal detection, especially for rare events with a high drug-attributable component, such as torsade de pointes (TdP). Use of different national SRSs is rarely attempted because of inherent difficulties, but should be considered on the assumption that rare events are diluted in international databases.

**Objective:** The aim was to describe TdP-related events associated with antipsychotics, H1-antihistamines and anti-infectives in three national SRSs (in Italy, Germany and France) and highlight potential signals of torsadogenicity through a combined literature evaluation.

**Methods:** A common search strategy was applied to extract TdP-related events: (1) TdP, (2) QT interval abnormalities, (3) ventricular fibrillation/tachycardia, and (4) sudden cardiac death. Signals of disproportionate reporting (SDRs) were calculated for TdP + QT interval abnormalities and defined by a lower limit of the 95% confidence interval of the reporting odds ratio (ROR) >1. Among SDRs with at least three cases without concomitant pro-arrhythmic drugs, we defined potential new signal of torsadogenicity as drugs with no published evidence from (a) the crediblemeds® website (http://www.crediblemeds.com, as of November 1st, 2014); (b) studies on the FDA Adverse Event Reporting System (FAERS); and (c) safety trials or pharmaco-epidemiological studies (as of December 16th, 2014).

**Results:** Overall, 3505 cases were retrieved (1372, 1468, and 801 for France, Germany and Italy, respectively). Antipsychotics were mainly recorded in Germany (792 cases), whereas antibiotics peaked at 515 and 491 (France and Italy, respectively). Forty-one drugs met criteria for SDRs in at least one single source, of which 31 were detected only from one single SRS: 18, ten and three (French, German and Italian SRS, respectively). By contrast, only five SDRs were detected in all national data sources (amisulpride, aripiprazole, haloperidol, olanzapine, risperidone). Overall, five potential new signals of torsadogenicity were identified: flupentixol, ganciclovir, levocetirizine, oxatomide and tiapride.

**Conclusions:** We found differences across and within national SRSs in the reporting of drug-induced TdP, which finally resulted in five potential new signals of torsadogenicity. These findings warrant targeted pharmacovigilance studies to formally assess the existence of actual drug-event associations.
Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase®
Ana Aldea Perona, Mar García-Sáiz, Emilio Sanz Álvarez

ABSTRACT

Introduction: In 2008, the US FDA issued an alert about an increased risk of psychiatric events associated with montelukast. Recent national pharmacovigilance analyses in Sweden, France and Spain detected a potential increase in reporting risk of the association.

Aim: Our objective was to analyse spontaneous reports of psychiatric events in children and adolescents worldwide treated with montelukast.

Methods: We conducted a retrospective analysis of Individual Case Safety Reports (ICSRs) recorded up to 1 January 2015 in the World Health Organization (WHO) database (VigiBase®), in which montelukast was associated with ‘psychiatric disorders’. We used the Bayesian Confidence Propagation Neural Network (BCPNN) approach for signal generation.

Results: A total of 14,670 ICSRs for montelukast were recorded, of which 2630 corresponded to psychiatric disorders in people aged <18 years. The main symptoms reported for infants (aged <2 years) were sleep disorders, for children (aged 2–11 years) the main symptoms were depression/anxiety, and for adolescents (aged 12–17 years) they were suicidal behaviour and depression/anxiety. Suicidal behaviour was over-represented in all age groups with information component (IC) values that reached 5.01 in children and 3.85 in adolescents. Unexpectedly, completed suicides were reported more frequently for children (IC: 3.15; IC025: 1.98) than for adolescents (IC: 3.11; IC025: 2.61) or the total population (IC 1.95; IC025: 1.73).

Conclusions: Neuropsychiatric disorders as side effects of montelukast were more frequently reported for children than for adults. Infants and children seem to be more prone to sleep disturbances, whereas adolescents present symptoms of depression/anxiety and psychotic reactions more often. Suicidal behaviour and completed suicide appear to be more frequently reported than previously thought in practice. Risk management plans and epidemiological studies are needed to quantify the risk. Practitioners should be aware of the risk of neuropsychiatric events associated with montelukast use, and should advise the patient and report new cases.
The Association between Potentially Inappropriate Prescribing and Medication-Related Hospital Admissions in Older Patients: A Nested Case Control Study

C. A. K. van der Stelt, A. M. A. Vermeulen Windsant-van den Tweel

ABSTRACT

Introduction: Medication-related problems can cause serious adverse drug events (ADEs) that may lead to hospitalization of the patient. There are multiple screening methods to detect and reduce potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs). Whether this will result in less medication-related hospitalizations is unknown. The study objective was to assess the risk of preventable medication-related hospital admissions associated with potentially inappropriate prescribing, using the Beers 2012 and the Screening Tool of Older Person’s Prescriptions and the Screening Tool to Alert doctors to Right Treatment (STOPP & START) 2008 criteria.

Design, setting and participants: A nested case-control study was conducted with a subset of Dutch participants from the Hospital Admissions Related to Medication (HARM) study. Cases were defined as patients aged ≥65 years with a potentially preventable medication-related hospital admission. For each case, one control was selected, matched for age and sex. The primary determinant was the presence of one or more PIMs according to the Beers 2012 and STOPP 2008 criteria. The secondary determinant was the presence of one or more PIMs and PPOs according to the STOPP & START 2008 criteria. The strength of the association between inappropriate prescribing and medication-related hospital admission was evaluated with multivariate logistic regression and expressed as odds ratios (ORs) with 95 % confidence intervals (CIs).

Results: The prevalence of Beers 2012 criteria PIMs in the total cohort was 44.4 %. The prevalence of STOPP & START 2008 criteria PIMs and PPOs were, respectively, 34.1 and 57.7 %. STOPP 2008 criteria PIMs were associated with preventable medication-related hospital admissions [OR adjusted for number of drugs and comorbidities (ORadj) 2.30, 95 % CI 1.30–4.07], whereas there was no association with Beers 2012 criteria PIMs (ORadj 1.49, 95 % CI 0.90–2.47). STOPP PIMs and START PPOs together were also associated with preventable medication-related hospital admissions (ORadj 3.47, 95 % CI 1.70–7.09).

Conclusion: Our study shows that patients with potentially inappropriate prescribing detected with the STOPP & START 2008 criteria are at risk of preventable medication-related hospital admissions. The STOPP & START 2008 criteria can be used to identify older people at risk of medication-related problems.
Sleeping pills, more formally defined as hypnotics, are sedatives used to induce and maintain sleep. In a review of publications for the past 30 years, descriptive epidemiologic studies were identified that examined the mortality risk of hypnotics and related sedative–anxiolytics. Of the 34 studies estimating risk ratios, odds ratios, or hazard ratios, excess mortality associated with hypnotics was significant (p < 0.05) in 24 studies including all 14 of the largest, contrasted with no studies at all suggesting that hypnotics ever prolong life. The studies had many limitations: possibly tending to overestimate risk, such as possible confounding by indication with other risk factors; confusing hypnotics with drugs having other indications; possible genetic confounders; and too much heterogeneity of studies for meta-analyses. There were balancing limitations possibly tending towards underestimates of risk such as limited power, excessive follow-up intervals with possible follow-up mixing of participants taking hypnotics with controls, missing dosage data for most studies, and over-adjustment of confounders. Epidemiologic association in itself is not adequate proof of causality, but there is proof that hypnotics cause death in overdoses; there is thorough understanding of how hypnotics euthanize animals and execute humans; and there is proof that hypnotics cause potentially lethal morbidities such as depression, infection, poor driving, suppressed respiration, and possibly cancer. Combining these proofs with consistent evidence of association, the great weight of evidence is that hypnotics cause huge risks of decreasing a patient’s duration of survival.

Appropriate Polypharmacy and Medicine Safety: When Many is not Too Many

Cathal A. Cadogan, Cristin Ryan, Carmel M. Hughes

The use of multiple medicines (polypharmacy) is increasingly common in middle-aged and older populations. Ensuring the correct balance between the prescribing of ‘many’ drugs and ‘too many’ drugs is a significant challenge. Clinicians are tasked with ensuring that patients receive the most appropriate combinations of medications based on the best available evidence, and that medication use is optimised according to patients’ clinical needs (appropriate polypharmacy). Historically, polypharmacy has been viewed negatively because of the associated medication safety risks, such as drug interactions and adverse drug events. More recently, polypharmacy has been identified as a risk factor for under-prescribing, such that patients do not receive necessary medications and this can also pose risks to patients’ safety and well-being. The negative connotations that have long been associated with the term polypharmacy could potentially be acting as a driving factor for under-prescribing, whereby clinicians are reluctant to prescribe necessary medicines for patients who are already receiving ‘many’ medicines. It is now recognised that the prescribing of ‘many’ medicines can be entirely appropriate in patients with several chronic conditions and that the risks of adverse drug events that have been associated with polypharmacy may be greatly reduced when patients’ clinical context is taken into consideration. In this article, we outline the current perspectives on polypharmacy and make the case for adopting the term ‘appropriate polypharmacy’ in differentiating between the prescribing of ‘many’ drugs and ‘too many’ drugs. We also outline the inherent challenges in doing so and provide recommendations for future clinical practice and research.
Testosterone Replacement Therapy and Mortality in Older Men

G. I. Hackett

ABSTRACT

While US testosterone prescriptions have tripled in the last decade with lower trends in Europe, debate continues over the risks, benefits and appropriate use of testosterone replacement therapy (TRT). Several authors blame advertising and the availability of more convenient formulations, whilst others have pointed out that the routine testing of men with erectile dysfunction (ED) (a significant marker of cardiovascular risk) and those with diabetes would inevitably increase the diagnosis of hypogonadism and lead to an increase in totally appropriate prescribing. They commented that this was merely an appropriate correction of previous under-diagnosis and under-treatment in line with evidence based guidelines. It is unlikely that persuasive advertising or convenient formulations could grow a market over such a sustained period if the treatment was not effective. Urologists and primary care physicians are the most frequent initiators of TRT usually for ED. Benefits are clearly established for sexual function, increase in lean muscle mass and strength, mood and cognitive function, with a possible reduction in frailty and osteoporosis. There remains no evidence that TRT is associated with increased risk of prostate cancer or symptomatic benign prostatic hyperplasia, yet the decision to initiate and continue therapy is often decided by urologists. The cardiovascular issues associated with TRT have been clarified by recent studies showing that therapy associated with clear increases in serum testosterone levels to the normal range is associated with reduced all-cause mortality. Studies reporting to show increased risk have been subject to flawed designs with inadequate baseline diagnosis and follow-up testing. Effectively, they have compared non-treated patients with under-treated or non-compliant subjects involving a range of different therapy regimes. Recent evidence suggests long-acting injections may be associated with decreased cardiovascular risk, but the transdermal route may be associated with potentially relatively greater risk because of conversion to dihydrotestosterone by the effect of 5-alpha reductase in skin. The multiple effects of TRT may add up to a considerable benefit to the patient that might be underestimatized by the physician primarily concerned with his own specialty. In a response to concerns about the possible risks associated with inappropriate prescribing expressed by Public Citizen, the Food and Drug Administration (FDA) published a complete refutation of all the concerns, only to issue a subsequent bulletin of concern over inappropriate use, whilst confirming the benefits in treating men with established testosterone deficiency. No additional evidence was provided for this apparent change of opinion, but longer term safety data on testosterone products were strongly suggested. In contrast, the European Medicines Agency (EMA), in November 2014, concluded that “there is no consistent evidence of increased cardiovascular risk with testosterone products”. This paper explores the most recent evidence surrounding the benefits and risks associated with TRT.
ABSTRACT

Introduction: Assessing the significance of pharmacist interventions (PIs) is essential to demonstrate the added value of pharmacists. Methods and tools for assessing the potential significance of PIs are diverse and their properties are questionable.

Objectives: We aimed to systematically review the tools available to assess the potential significance of PIs.

Methods: We conducted a systematic search for English- or French-language publications from 1986 to 2013 in PubMed, PsycINFO, PASCAL, and CINAHL. Studies were screened by two independent reviewers based on inclusion/exclusion criteria and were abstracted for content, structure of tools, and validation process.

Results: Of 873 citations screened, 82 distinct tools were identified from 133 studies. While clinical aspects were often defined quite clearly, terminology regarding humanistic, economic, and process-related aspects of PIs was omitted, incomplete, or ambiguous in most tools. The probabilities of consequences of PIs/drug-related problems were evaluated in 20/82 tools. Few tools simultaneously measured economic, clinical, humanistic, and process-related variables. Structure of the tools varied from an implicit, mono-dimensional tool to an explicit, multi-dimensional algorithm. Validation processes were diverse in terms of quantification and number of raters, rating method, and psychometric parameters. Of 133 identified studies, there was limited evidence of validity (8/133, 6.0 %), inter-rater reliability (49/133, 36.8 %), and intra-rater reliability (2/133, 1.5 %).

Conclusions: The majority of tools focused primarily on assessing clinical aspects and failed to detect comprehensive impacts. The heterogeneity of tools and assessment processes hindered our ability to synthesize the results of evaluations. Limited results for their validity and reliability cast doubt on the credibility of this methodology for justification of the value of PIs. Recommendations for development of tools with optimal theoretical, pragmatic, and psychometric properties are proposed.
Safety of Dalbavancin in the Treatment of Skin and Skin Structure Infections: A Pooled Analysis of Randomized, Comparative Studies
Michael W. Dunne, George H. Talbot, Helen W. Boucher, Mark Wilcox

ABSTRACT

Introduction: Dalbavancin is a new lipoglycopeptide that is active against Gram-positive pathogens, including methicillin-resistant Staphylococcus aureus. It has a half-life of 14.4 days, permitting intravenous treatment of acute bacterial skin and skin structure infections without the need for daily dosing.

Objective: The objective of these analyses was to compare the adverse event profile of dalbavancin with that of the comparator agents in the treatment of skin and skin structure infections.

Methods: Data on adverse events and laboratory assessments collected from 3002 patients enrolled in seven late-stage, randomized clinical trials were analyzed for patients receiving dalbavancin or a comparator antibiotic.

Results: Overall adverse event rates were similar or lower for patients receiving dalbavancin (799/1778; 44.9 %) compared with those receiving comparator agents (573/1224; 46.8 %, p = 0.012). The most common treatment-emergent adverse events were nausea, headache, diarrhea, constipation, vomiting, rash, urinary tract infection, pruritus, and insomnia. The duration and timing of the onset of adverse events were similar for patients receiving dalbavancin relative to the comparators.

Conclusion: Dalbavancin exhibits a favorable overall safety profile for treatment of acute bacterial skin and skin structure infections due to Gram-positive bacteria.

Adverse Drug Reactions Reported to a National HIV & Tuberculosis Health Care Worker Hotline in South Africa: Description and Prospective Follow-Up of Reports
Christine Njuguna, Annemie Stewart, Johannes P. Mouton, Marc Blockman

ABSTRACT

Introduction: The National HIV & Tuberculosis Health Care Worker (HCW) Hotline provides advice on the management of suspected adverse drug reactions (ADRs). We describe suspected ADRs reported to the hotline by HCWs, concordance with advice, and patient outcomes.

Methods: We reviewed suspected ADRs in HIV-infected patients, patients taking antiretrovirals and patients taking anti-tuberculosis therapy reported from May 2013 to October 2014. We performed causality assessment using the World Health Organization Uppsala Monitoring Centre (WHO-UMC) criteria. We included suspected ADRs categorized as certain, probable or possible in further analysis.

Results: We received 772 ADR reports, of which 87/772 (11.3 %) were classified as certain, 176/772 (22.8 %) as probable, 361/772 (46.8 %) as possible, and 148/772 (19.2 %) as unlikely or unassessable. The most frequent ADRs were rash, drug-induced liver injury (DILI) and kidney injury, comprising 110/624 (17.6 %), 87/624 (13.9 %), and 77/624 (12.3 %), respectively. The ADR was severe in 27.3 % of rashes, 36.4 % of kidney injury reports and 88.5 % of DILI reports. Most frequently implicated drugs, either alone or in combination with other potentially causative drugs, were efavirenz (rashes), efavirenz and anti-tuberculosis drugs (DILI) and tenofovir (kidney injury). In 383 cases with HCW follow-up, 254 (66.3 %) improved, 9 (2.3 %) had complete resolution, 32 (8.4 %) remained unchanged, 6 (1.6 %) deteriorated, 10 (2.6 %) died and 72 (18.8 %) had unknown outcome. Advice provided was followed in 93.2 % of these cases. Of 223 ADRs with preventability data, 40 (17.9 %) were preventable.

Conclusion: Queries about rashes, DILIs and kidney injuries were common. Detection and management of these ADRs should be included in HCW training. In cases with follow-up, concordance with advice was high, and HCWs reported improvement in the majority.
**ABSTRACT**

**Introduction:** As part of its mission, the US Food and Drug Administration (FDA) communicates with the public regularly about the benefits and risks of prescription and over-the-counter (OTC) drugs. Effectively communicating risk, however, is a significant public health challenge.

**Objective:** To better understand how different populations understand information communicated by the FDA about drug safety, we conducted a randomized experiment to examine comprehension and other measures of effectiveness of drug safety messages that occurred in a post-market surveillance phase.

**Methods:** We used an Internet panel survey of 1244 consumers, of whom 58 % used prescription drugs in the past year. Half of the sample panel was randomized to read a previous FDA Drug Safety Communication (DSC) with the drug name changed, and the other half was randomized to read a revised version of the same DSC. We examined how making certain modifications to the way drug risk information is communicated has an impact on comprehension and behavioral intentions, including the user’s likelihood of discontinuing the drug. We also studied how comprehension varied by respondent characteristics, health literacy skills, risk perceptions, and trust in the message.

**Results:** Based on a five-item comprehension index, the revised version of the message was associated with significantly greater comprehension of the information relative to the standard version (63 vs 52 % correct, p < 0.001). Significantly more respondents found the revised version to be clear (82 vs 73 %, p < 0.000), while fewer in that group reported learning something new (78 % vs 84 %, p = 0.015). No significant differences emerged between the two groups in terms of the message being informative, convincing, or helpful. We found no significant differences between the two groups in terms of behavioral intentions, risk perception, and trust.

**Conclusions:** We found that making plain language changes to the DSC significantly increased consumers’ level of comprehension of its content, providing support for ongoing use and further exploration of these strategies in pharmacovigilance communication research. The study findings have important implications for future drug safety and other communication messages related to prescription drugs.
Traceability of Biologics in the Netherlands: An Analysis of Information-Recording Systems in Clinical Practice and Spontaneous ADR Reports

Kevin Klein, Joep H. G. Scholl, Niels S. Vermeer, André W. Broekmans

ABSTRACT

Introduction and Objective: Pharmacovigilance requirements for biologics mandate that EU Member States shall ensure that any biologic that is the subject of a suspected adverse drug reaction (ADR) is identifiable by brand name and batch number. Recent studies showed that brand name identification is well established, whereas batch numbers are (still) poorly reported. We evaluated information-recording systems and practices in the Dutch hospital setting to identify determinants for brand name and batch number recording as well as success factors and bottlenecks for traceability.

Methods: We surveyed Dutch hospital pharmacists with an online questionnaire on systems and practices in hospitals for recording brand names and batch numbers. Additionally, we performed an analysis of the traceability of recombinant biologics in spontaneous ADR reports (received between 2009 and 2014) from the Netherlands Pharmacovigilance Centre Lareb.

Results: The survey showed that brand names are not routinely recorded in the clinical practice of Dutch hospitals, whereas batch numbers are poorly recorded. Seventy-six percent of the 1523 ADR reports for recombinant biologics had a traceable brand name whereas 5% of these reports contained a batch number. The results suggest a possible relationship between the availability of brand and batch number information in clinical practice and the inclusion of this information in ADR reports for biologics.

Conclusion: The limited traceability of brand names and batch numbers in ADR reports may be primarily caused by the shortcomings in the recording of information in clinical practice. We recommend efforts to improve information-recording systems as a first step to improve the traceability of biologics in ADR reporting.

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Risk of Inflammatory Bowel Disease with Oral Contraceptives and Menopausal Hormone Therapy: Current Evidence and Future Directions

Hamed Khalili

ABSTRACT

Crohn’s disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases, are archetypical inflammatory disorders of the gastrointestinal tract with rising incidence worldwide. Although the role of genetic factors in disease development has been highlighted by genome-wide association studies, environmental risk factors likely play a pivotal role in development of CD and UC. Prior observational studies have suggested a link between exogenous hormone use and risk of CD and UC. Specifically, studies have shown an association between oral contraceptive use and risk of CD and menopausal hormone therapy and risk of UC. Although the exact mechanism of these associations is largely unknown, a number of hypotheses have been proposed. First, oral estrogen has been shown to modify intestinal permeability, a critical step in the pathophysiology of inflammatory bowel disease. Second, exogenous hormone use through its effect on endogenous levels of hormones may enhance the development of Th1- and Th2-mediated inflammatory diseases. Lastly, recent data have linked modification in the gut microbiome to endogenous levels of androgens, which are also known to be altered with exogenous hormone use and influence the development of autoimmune diseases. This supports the intriguing hypothesis that the gut microbiome lies at the crossroads of pathways linking exogenous hormone use with innate and adaptive immunity. Future studies should therefore focus on bridging these epidemiologic findings to disease pathogenesis through comprehensive understanding of the complex interaction between exogenous hormone use, sex steroid biomarkers, genetic risk loci, and alterations in the intestinal microbial environment in the etiology of CD and UC.
Hepatotoxicity Associated with the Use of Anti-TNF-α Agents
Joshua B. French, Maurizio Bonacini, Marwan Ghabril, David Foureau

ABSTRACT

Medications to inhibit the actions of tumour necrosis factor alpha have revolutionized the treatment of several pro-inflammatory autoimmune conditions. Despite their many benefits, several serious side effects exist and adverse reactions do occur from these medications. While many of the medications’ potential adverse effects were anticipated and recognized in clinical trials prior to drug approval, several more rare adverse reactions were recorded in the literature as the popularity, availability and distribution of these medications grew. Of these potential adverse reactions, liver injury, although uncommon, has been observed in some patients. As case reports accrued over time and ultimately case series developed, the link became better established between this family of medicines and various patterns of liver injury. Interestingly, it appears that the majority of cases exhibit an autoimmune hepatitis profile both in serological markers of autoimmune liver disease and in classic autoimmune features seen on hepatic histopathology. Despite the growing evidence of this relationship, the pathogenesis of this reaction remains incompletely understood, but it appears to depend on characteristics of the medications and the genetic composition of the patients; it is likely more complicated than a simple medication class effect. Because of this still incomplete understanding and the infrequency of the occurrence, treatments have also been limited, although it is clear that most patients improve with cessation of the offending agent and, in certain cases, glucocorticoid use. However, more needs to be done in the future to unveil the underlying mechanisms of this adverse reaction.

Renal and Bone Adverse Effects of a Tenofovir-Based Regimen in the Treatment of HIV-Infected Children: A Systematic Review
Rose I. Okonkwo, Anita E. Weidmann, Emmanuel E. Effa

ABSTRACT

Introduction: Tenofovir disoproxil fumarate (TDF)-containing regimens in the treatment of HIV-infected children have safety concerns with respect to renal and bone toxicity.

Objective: The aim of this study was to systematically review and critically appraise the literature relating to the reported renal and bone adverse effects of TDF-based regimens in the treatment of HIV-infected children from 2 to 19 years old.

Methods: Searches were performed using the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE, OvidSP, ScienceDirect and Web of Science databases and platforms. All primary studies involving tenofovir use in HIV-infected children were sought. Studies that involved the use of TDF for pre- and post-exposure prophylaxis, and treatment of chronic hepatitis B virus infection were excluded. Data on study characteristics, participant’s characteristics, therapeutic intervention and adverse effects were extracted using a piloted tool. In addition, pharmacovigilance data from the WHO Adverse Reaction database were included.

Results: We identified 19 studies that reported the presence of renal and bone adverse effects of TDF and these included a total of 1100 study participants. The reports were in distinctly heterogeneous participant groups. A total of 287 renal and bone adverse effects were reported (250 renal and 37 bone adverse effects). Approximately 238 (21.6 %) participants were affected by these adverse effects. Of these, 15 participants stopped their TDF-containing regimen due to these adverse effects.

Conclusion: This systematic review summarises the reports of renal and bone adverse effects of a TDF-containing regimen in the treatment of HIV-infected children. Our findings suggest that the benefits of using TDF in children need to be balanced against the potential risk of toxicity.
Post-Marketing Benefit–Risk Assessment of Rotavirus Vaccination in Japan: A Simulation and Modelling Analysis
Edouard Ledent, Alfons Lieftucht, Hubert Buyse, Keiji Sugiyama

ABSTRACT

Introduction: Rotarix™, GSK’s live attenuated rotavirus vaccine, was introduced in Japan in 2011. A recent trend in reduction of rotavirus gastroenteritis (RVGE) due to this vaccine was described. However, an observed/expected analysis showed a temporal association with intussusception within 7 days post dose 1.

Objective: In this paper, we compare the benefit and risk of vaccination side-by-side in a benefit–risk analysis.

Methods: The number of vaccine-preventable RVGE-associated hospitalizations and deaths (benefit) and intussusception-associated hospitalizations and deaths (risk) following two doses of Rotarix™ in Japan was compared using simulations. Source data included peer-reviewed clinical and epidemiological publications, Japanese governmental statistics (Statistics Bureau, Ministry of Internal Affairs and Communications), and market survey data.

Results: For a birth cohort of 1 million vaccinated Japanese children followed for 5 years, the benefit–risk analysis suggested that the vaccine would prevent ~17,900 hospitalizations and ~6.3 deaths associated with RVGE. At the same time, vaccination would be associated with about ~50 intussusception hospitalizations and ~0.017 intussusception deaths. Therefore, for every intussusception hospitalization caused by vaccination and for one intussusception-associated death, 350 (95 % CI 69–2510) RVGE-associated hospitalizations and 366 (95 % CI 59–3271) RVGE-associated deaths are prevented, respectively, by vaccination.

Conclusions: The benefit–risk balance for Rotarix™ is favorable in Japan. From a public health perspective, the benefits in terms of prevented RVGE hospitalizations and deaths for the vaccinated population far exceed the estimated risks due to intussusception.
Social Media Mining for Toxicovigilance: Automatic Monitoring of Prescription Medication Abuse from Twitter
Abeed Sarker, Karen O’Connor, Rachel Ginn, Matthew Scotch, Karen Smith

ABSTRACT

Introduction: Prescription medication overdose is the fastest growing drug-related problem in the USA. The growing nature of this problem necessitates the implementation of improved monitoring strategies for investigating the prevalence and patterns of abuse of specific medications.

Objectives: Our primary aims were to assess the possibility of utilizing social media as a resource for automatic monitoring of prescription medication abuse and to devise an automatic classification technique that can identify potentially abuse-indicating user posts.

Methods: We collected Twitter user posts (tweets) associated with three commonly abused medications (Adderall®, oxycodone, and quetiapine). We manually annotated 6400 tweets mentioning these three medications and a control medication (metformin) that is not the subject of abuse due to its mechanism of action. We performed quantitative and qualitative analyses of the annotated data to determine whether posts on Twitter contain signals of prescription medication abuse. Finally, we designed an automatic supervised classification technique to distinguish posts containing signals of medication abuse from those that do not and assessed the utility of Twitter in investigating patterns of abuse over time.

Results: Our analyses show that clear signals of medication abuse can be drawn from Twitter posts and the percentage of tweets containing abuse signals are significantly higher for the three case medications (Adderall®: 23 %, quetiapine: 5.0 %, oxycodone: 12 %) than the proportion for the control medication (metformin: 0.3 %). Our automatic classification approach achieves 82 % accuracy overall (medication abuse class recall: 0.51, precision: 0.41, F measure: 0.46). To illustrate the utility of automatic classification, we show how the classification data can be used to analyze abuse patterns over time.

Conclusion: Our study indicates that social media can be a crucial resource for obtaining abuse-related information for medications, and that automatic approaches involving supervised classification and natural language processing hold promises for essential future monitoring and intervention tasks.
Clinicians’ Reports in Electronic Health Records versus Patients’ Concerns in Social Media: A Pilot Study of Adverse Drug Reactions of Aspirin and Atorvastatin
Maxim Topaz, Kenneth Lai, Neil Dhopeshwarkar, Diane L. Seger, Roee Sa’adon

ABSTRACT

Introduction: Large databases of clinician reported (e.g., allergy repositories) and patient reported (e.g., social media) adverse drug reactions (ADRs) exist; however, whether patients and clinicians report the same concerns is not clear.

Objectives: Our objective was to compare electronic health record data and social media data to better understand differences and similarities between clinician-reported ADRs and patients’ concerns regarding aspirin and atorvastatin.

Methods: This pilot study explored a large repository of electronic health record data and social media data for clinician-reported ADRs and patients concerns for two common medications: aspirin (n = 31,817 ADRs accessible in clinical data; n = 19,186 potential ADRs accessible in social media data) and atorvastatin (n = 15,047 ADRs accessible in clinical data; n = 23,408 potential ADRs accessible in social media data).

Results: We found that the most frequently reported ADRs matched the most frequent patients’ concerns. However, several less frequently reported reactions were more prevalent on social media (i.e., aspirin-induced hypoglycemia was discussed only on social media). Overall, we found a relatively strong positive and statistically significant correlation between the frequency ranking of reactions and patients’ concerns for atorvastatin (Pearson’s r = 0.61, p < 0.001) but not for aspirin (Pearson’s r = 0.1, p = 0.69).

Conclusion: Future studies should develop further natural language methods for a more detailed data analysis (i.e., identifying causality and temporal aspects in the social media data).

Use of Prescription Drug Samples in the USA: A Descriptive Study with Considerations for Pharmacoepidemiology
Christian Hampp, Patty Greene, Simone P. Pinheiro

ABSTRACT

Introduction: Free prescription drug samples provided in physician offices can lead to exposure misclassification in pharmacoepidemiologic studies that rely on pharmacy claims data.


Results: Between 2009 and 2013, a total of 44.7 % of newly initiated brand-only sitagliptin but only 3.6 % of generically available metformin therapy was provided as samples. We observed similar discrepancies between newly initiated rosuvastatin and simvastatin, dabigatran and warfarin, atomoxetine and methylphenidate, and between oral antibiotic drugs. During continued therapy, sample use was still present though to a lesser extent (sitagliptin 17.0 %, rosvastatin 23.9 %), and remained high for some oral contraceptives (norethindrone 55.8 %). Oral contraceptives had the longest average days of sample supply (levonorgestrel, continued use 85.1 days). The average days of supply for all other chronically used study drugs ranged from 13.4 (dabigatran, new use) to 25.3 (exenatide, continued use) per sample provided. From 1993 to 2013, we found pronounced drops in sample provisions over time coinciding with more recent generic approval dates.

Conclusions: We observed markedly differential exposure to medication samples between branded and generic drugs. This can introduce bias in pharmacoepidemiologic studies, especially when adverse events that occur soon after drug initiation are of interest.
ABSTRACT

Introduction: The two methods for minimizing competition bias in signal of disproportionate reporting (SDR) detection—masking factor (MF) and masking ratio (MR)—have focused on the strength of disproportionality for identifying competitors and have been tested using competitors at the drug level.

Objectives: The aim of this study was to develop a method that relies on identifying competitors by considering the proportion of reports of adverse events (AEs) that mention the drug class at an adequate level of drug grouping to increase sensitivity (Se) for SDR unmasking, and its comparison with MF and MR.

Methods: Reports in the French spontaneous reporting database between 2000 and 2005 were selected. Five AEs were considered: myocardial infarction, pancreatitis, aplastic anemia, convulsions, and gastrointestinal bleeding; related reports were retrieved using standardized Medical Dictionary for Regulatory Activities (MedDRA®) queries. Potential competitors of AEs were identified using the developed method, i.e. Competition Index (ComIn), as well as MF and MR. All three methods were tested according to Anatomical Therapeutic Chemical (ATC) classification levels 2–5. For each AE, SDR detection was performed, first in the complete database, and second after removing reports mentioning competitors; SDRs only detected after the removal was unmasked. All unmasked SDRs were validated using the Summary of Product Characteristics, and constituted the reference dataset used for computing the performance for SDR unmasking (area under the curve [AUC], Se).

Results: Performance of the ComIn was highest when considering competitors at ATC level 3 (AUC: 62 %; Se: 52 %); similar results were obtained with MF and MR.

Conclusion: The ComIn could greatly minimize the competition bias in SDR detection. Further study using a larger dataset is needed.


Pharmacovigilance is … Vigilance

I. Ralph Edwards, Rachida Soulayamani Bencheikh

ABSTRACT

The world changes continuously and pharmacovigilance as a new discipline also must change. There are new fields opening with novel challenges whilst we are still perfecting ways to manage and improve the basic challenges such as inadequate data for decision making and under-reporting. Traditional medicines, vaccines, poisoning and medication error are all aspects of the safety of medicines that we have monitored for decades, though without perhaps paying enough attention to their special aspects. There are many new stakeholders taking serious interest in pharmacovigilance outside the regulatory sphere and they often focus on improving individual patient care, rather than the more traditional concentration on broad public health. The same stakeholders are also drawing attention to other iatrogenic outcomes that should be recognised, evaluated and their outcomes compared and contrasted with medication, such as harm from medical devices. The vigilance methods used for medication are very much applicable to all these new fields, though more and different expertise will be needed to evaluate outcomes.
Comparative Safety and Tolerability of Prostacyclins in Pulmonary Hypertension

Caroline O’Connell, David Amar, Athénaïs Boucly, Laurent Savale, Xavier Jaïs

ABSTRACT

Prostacyclin (PGI2) is a prostaglandin derived from arachidonic acid in the endothelium and smooth muscle which causes vasodilation, inhibits platelet aggregation, and has anti-inflammatory, anti-thrombotic and anti-proliferative effects. In pulmonary arterial hypertension (PAH), PGI2 levels and PGI2 synthase expression are reduced, contributing to the vasoconstriction and vascular smooth muscle cell proliferation seen in the disease. Based on these findings, PGI2 analogues were developed to target this pathway. Epoprostenol was the first targeted therapy available for treating PAH. Due to the short half-life of this drug, it requires administration via a continuous intravenous infusion, and therefore it carries the risks of central line infections and thrombosis. However, it remains the treatment of choice in patients with severe PAH as it has a proven survival benefit as well as improved functional class and exercise capacity. Subsequently, several other PGI2 analogues have been developed with differing modes of administration and varying degrees of efficacy. Beraprost is an oral PGI2 analogue for which a sustained efficacy has not been demonstrated. Iloprost is a nebulised PGI2 analogue that requires administration six to nine times a day and leads to improved functional class, exercise capacity and haemodynamics. There are inhaled, oral, subcutaneous and intravenous forms of treprostinil. Subcutaneous treprostinil avoids the risks of a continuous intravenous administration; however, this drug can cause intractable pain at the injection site. Selexipag is the new oral non-prostanoid IP prostacyclin receptor agonist that has shown improved haemodynamics and good tolerance in a phase II study. Initial results of the phase III trial are promising. Comparison of the different PGI2 agents is limited by a lack of head-to-head clinical trials. However, the development of PGI2 analogues has improved survival in patients with PAH and remains the main treatment option in advanced disease. While PGI2 analogues have good efficacy in PAH, they are not interchangeable, and their delivery systems have many limitations; in particular, they are associated with significant deleterious consequences. In the future, it is hoped that the elusive goal of developing an effective oral PGI2 analogue will be achieved. This would increase the number of people who could benefit from the treatment while reducing the associated adverse events, and as a result improve the survival and quality of life for these patients.

Quantitative Risk–Benefit Analysis of Probiotic Use for Irritable Bowel Syndrome and Inflammatory Bowel Disease

William E. Bennett Jr.

ABSTRACT

Probiotics have seen widespread use for a variety of gastrointestinal problems, especially in two common disorders: irritable bowel syndrome and inflammatory bowel disease. Since a wide variety of probiotic preparations has been used, and despite a large number of studies performed, a great deal of heterogeneity exists among them. Straightforward evidence-based recommendations for the use of probiotics in irritable bowel syndrome and inflammatory bowel disease have thus been difficult to formulate. In an effort to improve understanding of the risk–benefit balance of probiotics in these conditions, this study (1) queried the US FDA Adverse Event Reporting System (FAERS) database for all reported adverse drug events related to probiotics in 2013, and (2) constructed risk–benefit planes for both irritable bowel syndrome and inflammatory bowel disease using a geometric approximation of the confidence region between risk and benefit. The results show that adverse events from probiotics vary widely by disease, and when they occur, they are mild and may be difficult to distinguish from the natural history of the underlying disorders they are used to treat. The risk–benefit plane for irritable bowel syndrome straddles the risk–benefit threshold, so patients can expect a balance between a low chance of risk and also a low chance of benefit. The risk–benefit plane for inflammatory bowel disease largely lies above the risk–benefit threshold, so patients may expect more benefit than risk in most cases. More standardized and high-quality research is needed to improve our understanding of risk and benefit for these complex biopharmaceuticals.
Risk of Seizures Associated with Antidepressant Use in Patients with Depressive Disorder: Follow-up Study with a Nested Case–Control Analysis Using the Clinical Practice Research Datalink

Marlene Bloechliger, Alessandro Ceschi, Stephan Rüegg, Hugo Kupferschmidt

ABSTRACT

Introduction: Antidepressant use has been associated with an increased risk of seizures. Evidence on the association between antidepressant use at therapeutic doses and seizures mainly comes from clinical trials that were not designed to investigate this potential relationship.

Objective: The objective of this study was to assess the risk of first-time seizures in association with exposure to antidepressants in patients with depressive disorders.

Methods: We conducted a retrospective follow-up study with a nested case–control analysis between 1998 and 2012, using data from the UK-based Clinical Practice Research Datalink (CPRD). We estimated crude incidence rates with 95% confidence intervals (CIs) of seizures in depressed patients who used selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), ‘other antidepressants’, no antidepressants, or who had used antidepressants in the past. To adjust for potential confounding, we estimated odds ratios of antidepressant drug use among cases with seizures and matched controls in a nested case–control analysis.

Results: Of 151,005 depressed patients, 619 had an incident seizure during follow-up. Incidence rates per 10,000 person-years were 12.44 (95% CI 10.67–14.21) in SSRI users, 15.44 (95% CI 8.99–21.89) in SNRI users, 8.33 (95% CI 4.68–11.98) in TCA users, 9.33 (95% CI 6.19–12.46) in non-users of antidepressants, and 5.05 (95% CI 4.49–5.62) in past users of antidepressants. In the case–control analysis, relative risk estimates for seizures were increased in current users of SSRIs (adjusted odds ratio 1.98, 95% CI 1.48–2.66) and SNRIs (adjusted odds ratio 1.99, 95% CI 1.20–3.29), but not TCAs (adjusted odds ratio 0.99, 95% CI 0.63–1.53), compared with non-users.

Conclusion: Current use of SSRIs or SNRIs was associated with a twofold increased risk of first-time seizures compared with non-use, while current use of TCAs (mostly low dose) was not associated with seizures. Treatment initiation in SSRI and SNRI users was associated with a higher risk of seizures than longer-term treatment.
Safety of Intranasal Quadrivalent Live Attenuated Influenza Vaccine (QLAIV) in Children and Adolescents: A Pilot Prospective Cohort Study in England

Rhian McNaughton, Elizabeth Lynn, Vicki Osborne, Abigail Coughtrie

ABSTRACT

**Introduction:** Fluenz Tetra is an intranasal quadrivalent live attenuated influenza vaccine (QLAIV) and is recommended as the vaccine of choice for children in the 2014/2015 influenza season vaccination programme in the UK.

**Objective:** The primary objective of the study was to estimate the crude incidence rate of adverse events of interest (AEIs) following vaccination with the nasal QLAIV early in the 2014/2015 influenza season in children and adolescents in England.

**Methods:** A pilot non-interventional cohort post-authorisation safety study (PASS) was conducted during the 2014/2015 influenza season in England. Vaccinees were recruited via the mass vaccination programme in England. Participant outcomes, validated by a healthcare professional (general practitioner) where appropriate, were captured through questionnaires (surface mail, telephone, e-questionnaire). Data analysis comprised descriptive statistics and calculation of event risks and incidence rates, stratified by age group and selected co-morbidities.

**Results:** The final evaluable cohort consisted of 385 participants; the median (interquartile range) age was 4 (3–9) years with a range of 2–17 years, and 53.2 % were female. The most frequently reported AEI was nasal congestion (n = 167; 43.4 %; 312.3 per 1000 patient-weeks [95 % CI 267.3–364.8]). Further frequently reported AEIs were malaise (n = 87; 22.6 %; 123.4 per 1000 patient-weeks [95 % CI 98.9–154.1]) and cough (n = 80; 20.8 %; 118.5 per 1000 patient-weeks [95 % CI 95.1–147.8]). Five hypersensitivity-type reactions were reported, although on follow-up none were true hypersensitivity reactions or required hospitalisation. No serious adverse events (SAEs) were reported, with no hospitalisations or deaths. No significant change in reactogenicity or other apparent safety signals was detected as part of this study.

**Conclusion:** The pilot study showed no significant change in reactogenicity or other apparent safety signals from the data collected. Continued enhanced surveillance of seasonal influenza vaccines will ensure their ongoing safety for the prevention of serious illness from seasonal influenza outbreaks.
Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®

Haggar H. Ampadu, Jarno Hoekman, Marieke L. de Bruin, Shanthi N. Pal

ABSTRACT

Introduction: Following the start of the World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) by 10 member countries in 1968, it took another 24 years for the first two African countries to join in 1992, by which time the number of member countries in the PIDM had grown to 33. Whilst pharmacovigilance (PV), including the submission of individual case safety reports (ICSR) to VigiBase®, the WHO global ICSR database, is growing in Africa, no data have been published on the growth of ICSR reporting from Africa and how the features of ICSRs from Africa compare with the rest of the world (RoW).

Objective: The objective of this paper was to provide an overview of the growth of national PV centres in Africa, the reporting of ICSRs by African countries, and the features of ICSRs from Africa, and to compare ICSRs from Africa with the RoW.

Methods: The search and analysis interface of VigiBase®—VigiLyze®—was used to characterise ICSRs submitted by African countries and the RoW. The distribution of ICSRs by African countries was listed and characterised by anatomic therapeutic chemical (ATC) code, Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) classification, and patient age and sex. The case-defining features of ICSRs between Africa and the RoW were also compared.

Results: The number of African countries in the PIDM increased from 2 in 1992 to 35 at the end of September 2015, and African PIDM members have cumulatively submitted 103,499 ICSRs (0.88% of global ICSRs) to VigiBase®. The main class of products in African ICSRs are nucleoside and nucleotide reverse transcriptase inhibitors (14.04%), non-nucleoside reverse transcriptase inhibitors (9.09%), antivirals for the treatment of HIV infections (5.50%), combinations of sulfonamides and trimethoprim (2.98%), and angiotensin-converting enzyme (ACE) inhibitors (2.42%). The main product classes implicated in ICSRs from the RoW are tumour necrosis factor-α (TNFα) inhibitors (5.29%), topical nonsteroidal anti-inflammatory preparations (2.26%), selective immunosuppressants (2.08%), selective serotonin reuptake inhibitors (2.04%) and HMG CoA reductase inhibitors (1.85%). The main SOCs reported from Africa versus the RoW include skin and subcutaneous tissue disorders (31.14% vs. 19.58%), general disorders and administration site conditions (20.91% vs. 30.49%) and nervous system disorders (17.48% vs. 19.13%). The 18–44 years age group dominated ICSRs from Africa, while the 45–64 years age group dominated the RoW. Identical proportions of females (57% Africa and the RoW) and males (37% Africa and the RoW) were represented.

Conclusions: As at the end of September 2015, 35 of 54 African countries were Full Member countries of the PIDM. Although the number of ICSRs from Africa has increased substantially, ICSRs from Africa still make up <1% of the global total in VigiBase®. The features of ICSRs from Africa differ to those from the RoW in relation to the classes of products as well as age group of patients affected. The gender of patients represented in these ICSRs are identical.
ABSTRACT

Introduction: The potential for routine sequence symmetry analysis (SSA) signal detection in health claims databases to detect new safety signals of medicines is unknown.

Objective: Our objective was to assess the potential utility of SSA as a signal detection tool in health claims data for detecting medicines with potential heart failure (HF) adverse event signals.

Methods: We applied the SSA method to all subsidized single-ingredient medicines in Australia. The source of data was the Australian Government Department of Veterans’ Affairs (DVA) administrative claims database using data collected between 2002 and 2011. We used first ever HF hospitalization and frusemide initiation as indicators for HF. A signal was considered to be present if the lower limit of the 95% confidence interval for the adjusted sequence ratio was greater than one. To identify potential new signals of HF, we excluded medicines where HF or edema was listed in the product information (PI) of that medicine or for any other medicine in the same class. We also excluded medicines that were used in HF treatment and medicines indicated for diseases that may contribute to the development of HF.

Results: We tested 691 medicines. HF signals were detected for 12% (80/691) using the hospitalization event and 22% (153/691) using frusemide initiation. Among medicines that did not have HF listed in the PI, SSA found 11% (44/397) associated with HF hospitalization and 15% (60/397) associated with frusemide initiation. Of the medicines tested in which no other medicine in the same class had HF or edema in the PI, and where the medicine was not indicated for a disease that is a risk factor for HF, potential new signals were generated for 2–3% of these medicines tested (12 of 397 medicines using HF hospitalization and 9 of 397 medicines using frusemide initiation).

Conclusion: SSA generated potential new signals of HF for some anti-glaucoma and anti-dyspepsia medicines. For some of the potential signals, the event is biologically plausible and some have pre-marketing and post-marketing case reports to support the finding. Confirmation of these signals using cohort studies is required.
Performance of Stratified and Subgrouped Disproportionality Analyses in Spontaneous Databases

Suzie Seabroke, Gianmario Candore, Kristina Juhlin, Naashika Quarcoo

ABSTRACT

Introduction: Disproportionality analyses are used in many organisations to identify adverse drug reactions (ADRs) from spontaneous report data. Reporting patterns vary over time, with patient demographics, and between different geographical regions, and therefore subgroup analyses or adjustment by stratification may be beneficial.

Objective: The objective of this study was to evaluate the performance of subgroup and stratified disproportionality analyses for a number of key covariates within spontaneous report databases of differing sizes and characteristics.

Methods: Using a reference set of established ADRs, signal detection performance (sensitivity and precision) was compared for stratified, subgroup and crude (unadjusted) analyses within five spontaneous report databases (two company, one national and two international databases). Analyses were repeated for a range of covariates: age, sex, country/region of origin, calendar time period, event seriousness, vaccine/non-vaccine, reporter qualification and report source.

Results: Subgroup analyses consistently performed better than stratified analyses in all databases. Subgroup analyses also showed benefits in both sensitivity and precision over crude analyses for the larger international databases, whilst for the smaller databases a gain in precision tended to result in some loss of sensitivity. Additionally, stratified analyses did not increase sensitivity or precision beyond that associated with analytical artefacts of the analysis. The most promising subgroup covariates were age and region/country of origin, although this varied between databases.

Conclusions: Subgroup analyses perform better than stratified analyses and should be considered over the latter in routine first-pass signal detection. Subgroup analyses are also clearly beneficial over crude analyses for larger databases, but further validation is required for smaller databases.

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Maximizing the Post-Approval Safety of Flibanserin: A Role for Regulators, Clinicians, and Patients

Sheriza N. Baksh, Walid F. Gellad, G. Caleb Alexander

ABSTRACT

In August 2015, the US Food and Drug Administration (FDA) made the controversial decision to approve flibanserin (Addyi®) for women experiencing hypoactive sexual desire disorder. A number of factors contributed to disagreements regarding the FDA’s decision, including the product’s two prior failed FDA reviews, the unmet need of women with this disorder, extensive advocacy and politicization surrounding the product’s relevance to women and sexual health, the potential for widespread off-label use, and the product’s tenuous risk/benefit profile. Despite that, attention now shifts to maximizing the safe use of the product, including the optimal means to avoid numerous drug–drug interactions as well as the concomitant use of alcohol, both of which potentiate the risks of dizziness, hypotension, and syncope. Although the FDA has implemented a comprehensive Risk Evaluation and Mitigation Strategies program to maximize the product’s safe use, patients, clinicians, and regulators must exhibit heightened vigilance early in the product’s post-market life.
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Dipeptidyl Peptidase (DPP)-4 Inhibitor-Induced Arthritis/Arthralgia: A Review of Clinical Cases
Annmaria Mascolo, Concetta Rafaniello, Liberata Sportiello, Maurizio Sessa

Dipeptidyl peptidase (DPP)-4 inhibitors are a class of oral drugs used for the treatment of type 2 diabetes mellitus (T2DM). The pharmacological inhibition of DPP-4 seems to also induce adverse events related to cytokine-induced inflammation. Recently, several clinical cases regarding the association of DPP-4 inhibitors and the onset of arthritis/arthralgia have been reported in the literature. Various mechanisms could be responsible for DPP-4 inhibitor-induced arthritis/arthralgia, and the increase of cytokines, chemokines, matrix metalloproteinases (MMPs) and genetic factors plays an important role. The US FDA published a safety announcement regarding the entire drug class, encouraging healthcare professionals and patients to pay attention to the occurrence of arthralgia during treatment with DPP-4 inhibitors; arthralgia could be assessed as a class adverse drug event for DPP-4 inhibitors. To summarize the evidence on the correlation between DPP-4 inhibitors and arthritis/arthralgia, and to explain the measures taken by the FDA with regard to arthralgia risk, we performed a literature review of recent evidence concerning this association. This review shows the necessity of other studies to better define the association between DPP-4 inhibitors and arthritis/arthralgia.
Safety Profile of Atorvastatin 80 mg: A Meta-Analysis of 17 Randomized Controlled Trials in 21,910 Participants

Haixia Li, Cailian Wang, Shuo Zhang, Sihao Sun, Ruifei Li, Meijuan Zou

ABSTRACT

Introduction: Atorvastatin 80 mg/day has significant benefits for the primary and secondary prevention of cardiovascular and cerebrovascular disease. To our knowledge, no meta-analysis focusing on assessing the safety profile of atorvastatin 80 mg/day has been performed; therefore, our aim was to evaluate the tolerability and adverse event (AE) patterns of this drug/dose.

Methods: We conducted a search of the Cochrane Library, EMBASE and PubMed databases through to July 2015 for randomized controlled trials (RCTs). The safety endpoints included the incidence of discontinuations due to AEs, transaminase elevation, creatine kinase (CK) elevation, myalgia and rhabdomyolysis. We also conducted subgroup analyses according to the length of follow-up and clinical condition.

Results: Data from 17 RCTs involving 21,910 participants were included. Pooled analyses showed that atorvastatin 80 mg/day was less tolerable [risk ratio (RR) 1.29, 95 % confidence interval (CI) 1.17–1.42] and increased the risk of transaminase elevation (RR 4.59, 95 % CI 3.26–6.48) compared with controls. No significant difference was observed between the two groups in terms of the incidence of CK elevation (RR 1.38, 95 % CI 0.97–1.95), myalgia (RR 1.06, 95 % CI 0.93–1.20), and rhabdomyolysis (RR 0.67, 95 % CI 0.19–2.36).

Conclusions: Patients treated with atorvastatin 80 mg/day, specifically patients with coronary artery disease (CAD), have a higher risk of transaminase elevation, which is not seen if patient exposure is less than 16 weeks. Atorvastatin 80 mg/day is less well-tolerated compared with controls, especially in patients with CAD, but an overall favorable tolerability profile is found if patient exposure is less than 52 weeks.
Evidence of Misclassification of Drug–Event Associations Classified as Gold Standard ‘Negative Controls' by the Observational Medical Outcomes Partnership (OMOP)

Manfred Hauben, Jeffrey K. Aronson, Robin E. Ferner

ABSTRACT

Introduction: Pharmacovigilance includes analysis of large databases of information on drugs and events using algorithms that detect disproportional frequencies of associations. In order to test such algorithms, attempts have been made to provide canonical reference lists of so-called ‘positive controls’ and ‘negative controls’. Reference sets with even modest levels of misclassification may result in under- or overstatement of the performance of algorithms.

Aim: We sought to determine the extent to which ‘negative control’ drug–event pairs in the Observational Medical Outcomes Partnership (OMOP) database are misclassified

Methods: We searched the medical literature for evidence of associations between drugs and events listed by OMOP as negative controls.

Results: The criteria used in OMOP to classify positive and negative controls are asymmetric; drug–event associations published only as case series or case reports are classified as positive controls if they are cited in Drug-Induced Diseases by Tisdale and Miller, but as negative controls if case series or case reports exist but are not cited in Tisdale and Miller. Of 233 drug–event pairs classified in the 2013 version of OMOP as negative controls, 21 failed to meet pre-specified OMOP adjudication criteria; in another 19 cases we found case reports, case series, or observational evidence that the drug and event are associated. Overall, OMOP misclassified, or may have misclassified, 40 (17 %) of all ‘negative controls.’

Conclusions: Results from studies of the performance of signal-detection algorithms based on the OMOP gold standard should be viewed with circumspection, because imperfect gold standards may lead to under/overstatement of absolute and relative signal detection algorithm performance. Improvements to OMOP would include omitting misclassified drug–event pairs, assigning more specific event labels, and using more extensive sources of information.
ABSTRACT

Introduction: Drug-induced prolongation of the QT interval on the electrocardiogram (long QT syndrome, LQTS) can lead to a potentially fatal ventricular arrhythmia known as torsades de pointes (TdP). Over 40 drugs with both cardiac and non-cardiac indications are associated with increased risk of TdP, but drug–drug interactions contributing to LQTS (QT-DDIs) remain poorly characterized. Traditional methods for mining observational healthcare data are poorly equipped to detect QT-DDI signals due to low reporting numbers and lack of direct evidence for LQTS.

Objective: We hypothesized that LQTS could be identified latently using an adverse event (AE) fingerprint of more commonly reported AEs. We aimed to generate an integrated data science pipeline that addresses current limitations by identifying latent signals for QT-DDIs in the US FDA’s Adverse Event Reporting System (FAERS) and retrospectively validating these predictions using electrocardiogram data in electronic health records (EHRs).

Methods: We trained a model to identify an AE fingerprint for risk of TdP for single drugs and applied this model to drug pair data to predict novel DDIs. In the EHR at Columbia University Medical Center, we compared the QTc intervals of patients prescribed the flagged drug pairs with patients prescribed either drug individually.

Results: We created an AE fingerprint consisting of 13 latently detected side effects. This model significantly outperformed a direct evidence control model in the detection of established interactions (p = 1.62E−3) and significantly enriched for validated QT-DDIs in the EHR (p = 0.01). Of 889 pairs flagged in FAERS, eight novel QT-DDIs were significantly associated with prolonged QTc intervals in the EHR and were not due to co-prescribed medications.

Conclusions: Latent signal detection in FAERS validated using the EHR presents an automated and data-driven approach for systematically identifying novel QT-DDIs. The high-confidence hypotheses flagged using this method warrant further investigation.
ABSTRACT

Introduction: Post-marketing safety surveillance primarily relies on data from spontaneous adverse event reports, medical literature, and observational databases. Limitations of these data sources include potential under-reporting, lack of geographic diversity, and time lag between event occurrence and discovery. There is growing interest in exploring the use of social media (‘social listening’) to supplement established approaches for pharmacovigilance. Although social listening is commonly used for commercial purposes, there are only anecdotal reports of its use in pharmacovigilance. Health information posted online by patients is often publicly available, representing an untapped source of post-marketing safety data that could supplement data from existing sources.

Objectives: The objective of this paper is to describe one methodology that could help unlock the potential of social media for safety surveillance.

Methods: A third-party vendor acquired 24 months of publicly available Facebook and Twitter data, then processed the data by standardizing drug names and vernacular symptoms, removing duplicates and noise, masking personally identifiable information, and adding supplemental data to facilitate the review process. The resulting dataset was analyzed for safety and benefit information.

Results: In Twitter, a total of 6,441,679 Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms (PTs) representing 702 individual PTs were discussed in the same post as a drug compared with 15,650,108 total PTs representing 946 individual PTs in Facebook. Further analysis revealed that 26 % of posts also contained benefit information.

Conclusion: Social media listening is an important tool to augment post-marketing safety surveillance. Much work remains to determine best practices for using this rapidly evolving data source.
Allergy-Like Immediate Reactions with Herbal Medicines: A Retrospective Study Using Data from VigiBase®

Jitka Pokladnikova, Ronald H. B. Meyboom, Ricarda Meincke, David Niedrig

ABSTRACT

Introduction: Herbal medicines are used worldwide and with an increasing popularity in Western countries. Although often perceived as ‘naturally safe’, herbals may cause severe adverse drug reactions (ADRs), with immediate allergic reactions being particularly life threatening.

Objectives: The aim of this study was to analyse immediate allergy-like ADRs to herbals documented in VigiBase®, the WHO international pharmacovigilance database.

Methods: The documentation of all suspected ADRs in association with herbal exposure reported to VigiBase® from 1969 to August 2014 was retrieved. Among all reports in which WHO-ART reaction terms were indicative of acute allergic reactions, those classified as ‘suspect’ with a documented causality assessment and latency time of ≤1 day were selected. For the most frequent specific herbal–ADR combinations, the information component (IC) as a measure of disproportionality based on Bayesian statistics was calculated.

Results: We identified 757 reports out of 1039 ADRs. Products with mixed herbals (36.0 %) as well as those administered orally (63.2 %) were predominant. The most frequent reactions were urticaria and rash (49.2 %). Anaphylactic reactions accounted for 9.5 %. Disproportionally frequent reporting of mouth edema (IC = 1.81) and anaphylactic reactions (IC = 1.24) to Phleum pretense were noted.

Conclusion: Our findings indicate that herbal medicines for oral use carry a risk of causing immediate allergy-like ADRs. Studies using the VigiBase® database can identify specific combinations of particular herbs and adverse reactions. Healthcare professionals and patients should be aware of these risks and report any serious adverse experiences.

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Good Signal Detection Practices: Evidence from IMI PROTECT

Antoni F. Z. Wisniewski, Andrew Bate, Cedric Bousquet, Andreas Brueckner

ABSTRACT

Over a period of 5 years, the Innovative Medicines Initiative PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) project has addressed key research questions relevant to the science of safety signal detection. The results of studies conducted into quantitative signal detection in spontaneous reporting, clinical trial and electronic health records databases are summarised and 39 recommendations have been formulated, many based on comparative analyses across a range of databases (e.g. regulatory, pharmaceutical company). The recommendations point to pragmatic steps that those working in the pharmacovigilance community can take to improve signal detection practices, whether in a national or international agency or in a pharmaceutical company setting. PROTECT has also pointed to areas of potentially fruitful future research and some areas where further effort is likely to yield less.
Medication Errors: New EU Good Practice Guide on Risk Minimisation and Error Prevention

Thomas Goedecke, Kathryn Ord, Victoria Newbould, Sabine Brosch, Peter Arlett

ABSTRACT

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Reducing the risk of medication errors is a shared responsibility between patients, healthcare professionals, regulators and the pharmaceutical industry at all levels of healthcare delivery. In 2015, the EU regulatory network released a two-part good practice guide on medication errors to support both the pharmaceutical industry and regulators in the implementation of the changes introduced with the EU pharmacovigilance legislation. These changes included a modification of the ‘adverse reaction’ definition to include events associated with medication errors, and the requirement for national competent authorities responsible for pharmacovigilance in EU Member States to collaborate and exchange information on medication errors resulting in harm with national patient safety organisations. To facilitate reporting and learning from medication errors, a clear distinction has been made in the guidance between medication errors resulting in adverse reactions, medication errors without harm, intercepted medication errors and potential errors. This distinction is supported by an enhanced MedDRA® terminology that allows for coding all stages of the medication use process where the error occurred in addition to any clinical consequences. To better understand the causes and contributing factors, individual case safety reports involving an error should be followed-up with the primary reporter to gather information relevant for the conduct of root cause analysis where this may be appropriate. Such reports should also be summarised in periodic safety update reports and addressed in risk management plans. Any risk minimisation and prevention strategy for medication errors should consider all stages of a medicinal product’s life-cycle, particularly the main sources and types of medication errors during product development. This article describes the key concepts of the EU good practice guidance for defining, classifying, coding, reporting, evaluating and preventing medication errors. This guidance should contribute to the safe and effective use of medicines for the benefit of patients and public health.

Safety Considerations with Dual Bronchodilator Therapy in COPD: An Update

Maria Gabriella Matera, Paola Rogliani, Luigino Calzetta, Mario Cazzola

ABSTRACT

Combining a long-acting β2-agonist (LABA) with a long-acting anti-muscarinic agent (LAMA) provides synergistic benefit on airway smooth muscle relaxation, which may have major implications for the use of LABA/LAMA combinations in the treatment of chronic obstructive pulmonary disease (COPD). There are four different approved LAMA/LABA fixed-dose combinations (FDCs)—glycopyrronium/indacaterol, umeclidinium/vilanterol, tiotropium/olodaterol, and aclidinium/formoterol—and another, glycopyrronium/formoterol, that is still under clinical development. Many pivotal trials have shown that all of these FDCs are more effective than monotherapies in inducing bronchodilation and do not amplify the possible adverse events (AEs) that are characteristic of LAMAs and LABAs when used as monotherapy. Unfortunately, these clinical trials have included a very small and highly selected fraction of the COPD patient population. Therefore, it is questionable whether such data can be extrapolated to a larger, ‘real-life’ population of patients with COPD, especially given that COPD patients with co-morbidities are often excluded from clinical trials, COPD is a major risk factor for most cardiovascular diseases, and both LAMAs and LABAs have a high potential to impact cardiac activities. All clinical trials have been conducted under widely varying conditions and, consequently, AE rates of a drug observed in a clinical trial cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. Head-to-head studies comparing the different LAMA/LABA FDCs that will include the true patients that we meet in our everyday practice are absolutely essential if we wish to make a therapeutic choice that is not purely empirical.
The Safety of Prochlorperazine in Children: A Systematic Review and Meta-Analysis
Melissa Lau Moon Lin, Paula D. Robinson, Jacqueline Flank, Lillian Sung

ABSTRACT

Introduction: Prochlorperazine is recommended for adults with breakthrough or refractory chemotherapy-induced nausea and vomiting (CINV). The objective of this review was to describe its safety in children when given for any indication to help define its role for CINV control in children.

Methods: Electronic searches of MEDLINE, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials were performed as of 9 March 2015. All studies in English reporting adverse effects (AEs) associated with prochlorperazine in children (≤18 years) were included. AEs were synthesized for prospective studies.

Results: Forty-nine (15 prospective) studies evaluating the use of prochlorperazine in 758 children were included. The most commonly reported AEs in prospective studies of prochlorperazine in children were sedation (multiple-dose studies: 10 %, 95 % CI 5–21) and extrapyramidal symptoms (EPS) (single-dose studies: 9 %, 95 % CI 3–29; multiple-dose studies: 4 %, 95 % CI 1–11). Serious AEs (seizure, neuroleptic malignant syndrome, autonomic collapse, tardive dyskinesia) were rarely associated with prochlorperazine use in children. Five fatalities were reported in children receiving prochlorperazine.

Limitations: The limitations of this systematic review and meta-analysis were that the AEs reported in the included studies were heterogeneous, the prospective use of systematic clinical tools to identify AEs was rare, and the risk of bias in most prospective studies was moderate.

Conclusions: The most common AEs reported with the pediatric use of prochlorperazine are EPS and sedation. Fatalities, life-threatening, and persistent AEs have also been reported.
ABSTRACT

Introduction: Intravitreal bevacizumab (IVTB) is used to treat age-related macular degeneration (ARMD), although its use is off-label and its cardiovascular safety has not been unequivocally established.

Objectives: Our objective was to assess the cardiovascular safety of IVTB in patients with ARMD.

Methods: We conducted a systematic review and meta-analysis of published randomized controlled trials (RCTs) and observational studies.

Results: Of the 2028 non-duplicate records, five RCTs versus ranibizumab (N = 3038, 12/24 months), four RCTs comparing different regimens (N = 809, 12/23 months), one RCT versus pegaptanib, photodynamic therapy (PDT), or sham (N = 131, 12 months), and three observational studies versus PDT, ranibizumab, or pegaptanib (~150,000 or 1666 patients/12 months and 317 patients/1–2 years, respectively) had a low risk of bias/high quality and ≥20 patients per arm with ≥6 months and ≥3 injections of treatment. RCT-based comparisons with PDT or pegaptanib are negligible. Observational data have not demonstrated differences [all-cause mortality, myocardial infarction (MI), stroke], but the level of evidence is “very low” (imprecise, indirect). RCT-based comparisons with ranibizumab did not demonstrate differences regarding some outcomes, although certain point estimates were at the level of a relevant harm/benefit [all-cause mortality odds ratio (OR) 1.103, 95 % confidence interval (CI) 0.641–1.898; vascular mortality OR 1.380, 95 % CI 0.476–3.997; MI OR 0.551, 95 % CI 0.265–1.146; stroke OR 0.657, 95 % CI 0.260–1.660; transitory ischemic attack OR 1.536, 95 % CI 0.444–5.313; atherothrombotic events (ATEs) OR 1.007, 95 % CI 0.641–1.593; venous thromboembolism OR 2.325, 95 % CI 0.963–5.612] or suggested a higher risk with bevacizumab (hypertension OR 7.512, 95 % CI 1.056–52.3), but estimates were based on sparse data, were extremely imprecise, and commonly exhibited considerable heterogeneity/inconsistency. The level of evidence per outcome was “low” or “very low”. Observational data did not demonstrate difference (all-cause mortality, MI, stroke), or suggested a higher risk with bevacizumab (ATE), but were imprecise and indirect (level of evidence “very low”). RCT-based comparisons of different IVTB regimens suffered from the same limitations.

Conclusion: Published data on IVTB in AMRD provide only a low level of evidence on its cardiovascular safety and do not support any finite conclusions.
Long-Term Outcomes of Short-Term Statin Use in Healthy Adults: A Retrospective Cohort Study
Ishak A. Mansi, Jenny English, Song Zhang, Eric M. Mortensen, Ethan A. Halm

ABSTRACT

Introduction: Data suggest that the beneficial cardiovascular effects of statins are maximized after the first year of statin use; yet, the timeline of statin-associated adverse events is not well delineated.

Objective: To examine the associations of short-term statin use (≤1 year) with short- and long-term adverse events and beneficial cardiovascular outcomes in a ‘healthy’ cohort.

Participants and Methods: A cohort study of a healthy Tricare population (fiscal year [FY] 2002 through FY 2011) who have no cardiovascular disease, major comorbidities requiring medications, or functional limitations. Statin users used statins for 90–365 days during FY 2005 as their only prescription medication. Nonusers had medical encounters but did not receive prescription medications during FY 2005, and did not receive any statins throughout the study period from FY 2002 to FY 2011. Outcomes were the occurrence of major acute cardiovascular events, diabetes mellitus and its complications, kidney diseases, musculoskeletal diseases, obesity, cataracts, malignancy, and death.

Results: We matched 1525 statin users to 1525 nonusers. During the follow-up period (FY 2006 to FY 2011), statin users had significantly higher odds of developing diabetes and diabetic complications that persisted throughout follow-up (odds ratio [OR] 1.93, 95% confidence interval [CI] 1.55–2.41 and OR 2.15, 95% CI 1.20–3.86, respectively). Short-term statin use was not associated with decreased odds of major acute cardiovascular events (OR 1.17, 95% CI 0.72–1.92). There were no differences in risks of kidney diseases, musculoskeletal diseases, or malignancy.

Conclusions: Short-term statin use for primary prevention in this healthy cohort was associated with an increased risk of long-term diabetes and diabetic complications without cardiovascular benefits. Further study using pragmatic studies and prospective observational studies appropriately equipped to eliminate unidentified confounders are urgently needed.
A Pharmacovigilance Signaling System Based on FDA Regulatory Action and Post-Marketing Adverse Event Reports
Keith B. Hoffman, Mo Dimbil, Nicholas P. Tatonetti, Robert F. Kyle

ABSTRACT

Introduction: Many serious drug adverse events (AEs) only manifest well after regulatory approval. Therefore, the development of signaling methods to use with post-approval AE databases appears vital to comprehensively assess real-world drug safety. However, with millions of potential drug–AE pairs to analyze, the issue of focus is daunting.

Objective: Our objective was to develop a signaling platform that focuses on AEs with historically demonstrated regulatory interest and to analyze such AEs with a disproportional reporting method that offers broad signal detection and acceptable false-positive rates.

Methods: We analyzed over 1500 US FDA regulatory actions (safety communications and drug label changes) from 2008 to 2015 to construct a list of eligible signal AEs. The FDA Adverse Event Reporting System (FAERS) was used to evaluate disproportional reporting rates, constrained by minimum case counts and confidence interval limits, of these selected AEs for 109 training drugs. This step led to 45 AEs that appeared to have a low likelihood of being added to a label by FDA, so they were removed from the signal eligible list. We measured disproportional reporting for the final group of eligible AEs on a test group of 29 drugs that were not used in either the eligible list construction or the training steps.

Results: In a group of 29 test drugs, our model reduced the number of potential drug–AE signals from 41,834 to 97 and predicted 73 % of individual drug label changes. The model also predicted at least one AE–drug pair label change in 66 % of all the label changes for the test drugs.

Conclusions: By concentrating on AE types with already demonstrated interest to FDA, we constructed a signaling system that provided focus regarding drug–AE pairs and suitable accuracy with regard to the issuance of FDA labeling changes. We suggest that focus on historical regulatory actions may increase the utility of pharmacovigilance signaling systems.
Universal Correction for QT/RR Hysteresis
Marek Malik, Lars Johannesen, Katerina Hnatkova, Norman Stockbridge

ABSTRACT

Introduction: Clinical pharmacology QT/QTc studies can be smaller if they more efficiently use the data generated.

Objective: The aim was to use large sets of electrocardiograms (ECGs) deposited at the US Food and Drug Administration to investigate the implications of heart rate measurement on the accuracy of QTc data.

Methods: Using the data of 80 thorough QT studies, we investigated whether placing study subjects in supine positions during short-term time points stabilizes heart rate (part I, based on 73 studies with 747,912 measured ECGs in 6786 healthy subjects) and whether heart rate measurements different from RR intervals captured simultaneously with QT intervals decrease QTc variability (part II, based on seven studies with 897,570 ECG measurements in 751 healthy subjects).

Results: In the part I data, when subjects were placed in supine undisturbed positions, heart rate instability (max–min of repeatedly measured heart rates within the same study time point) exceeding 5 beats per minute (bpm) was observed 40% of the time and exceeded 10 bpm 10% of the time. In the part II data, even when including QT measurements preceded by variable heart rates, correction of QT durations for RR interval values derived through a simple QT/RR hysteresis model with 95% adaptation in 120 s led to mean intra-subject standard deviation of QTc (Fridericia formula) of only 7.14 ± 1.98 and 6.38 ± 1.50 ms in women and men, respectively.

Conclusion: The QT/RR hysteresis model with 95% adaptation in 120 s is universally applicable to healthy subjects, providing small QTc variability. Supine positions do not generally stabilize heart rates in healthy subjects.

Pharmacokinetics, Efficacy, and Safety of Hepatitis C Virus Drugs in Patients with Liver and/or Renal Impairment
Elise J. Smolders, Clara T. M. M. de Kanter, Bart van Hoek, Joop E. Arends

ABSTRACT

Hepatitis C virus (HCV)-infected patients often suffer from liver cirrhosis, which can be complicated by renal impairment. Therefore, in this review we describe the treatment possibilities in HCV patients with hepatic and renal impairment. Cirrhosis alters the structure of the liver, which affects drug-metabolizing enzymes and drug transporters. These modifications influence the plasma concentration of substrates of drugs metabolized/transported by these enzymes. The direct-acting antivirals (DAAs) are substrates of, for example, cytochrome P450 enzymes in the liver. Most DAAs are not studied in HCV-infected individuals with decompensated cirrhosis, and therefore awareness is needed when these patients are treated. Most DAAs are contraindicated in cirrhotic patients; however, patients with a Child-Pugh score of B or C can be treated safely with a normal dose sofosbuvir plus ledipasvir or daclatasvir, in combination with ribavirin. Patients with renal impairment (glomerular filtration rate [GFR] <90 mL/min) or who are dependent on dialysis often tolerate ribavirin treatment poorly, even after dose adjustments. However, most DAAs can be used at the normal dose because DAAs are not renally excreted. To date, grazoprevir plus elbasvir is the preferred DAA regimen in patients with renal impairment as data are pending for sofosbuvir patients with GFR <30 mL/min (as for ledipasvir and velpatasvir). However, sofosbuvir has been used in a small number of patients with severe renal impairment and, based on these trials, we recommend sofosbuvir 400 mg every day when no other DAA regimen is available. Ledipasvir and velpatasvir are not recommended in patients with severe renal impairment.
ABSTRACT

Numerous preclinical and clinical studies investigating the neurodevelopmental and neurocognitive effects of exposure to anesthesia and the combination of anesthesia and surgery have demonstrated histopathological and both temporary and long-term cognitive and behavioral effects at the extremes of the human age spectrum. Increasing coverage in the lay press for both our youngest and oldest patient populations has led to heightened concerns regarding the potential harmful side effects of almost all commonly used anesthetic drug regimens. Although the majority of information regarding anesthetic risks in the developing brain derives from preclinical work in rodents, research involving the aged brain has identified a well-defined postoperative cognitive phenotype in humans. While preclinical and clinical data appear to support some association between anesthesia and surgery and the development of detrimental cognitive changes in both the developing and the aged brain, correlation between anesthesia and surgery and poor neurological outcomes does not imply causation. Given this information, no single anesthetic or group of anesthetics can be recommended over any other in terms of causing or preventing negative neurocognitive outcomes in either population. This review summarizes the growing body of preclinical and clinical literature dedicated to the detrimental effects of anesthesia on both the developing and the aging brain.

Safety and Tolerability of Pharmacological Treatment of Alcohol Dependence: Comprehensive Review of Evidence

Julia M. A. Sinclair, Sophia E. Chambers, Celia J. Shiles, David S. Baldwin

ABSTRACT

Alcohol use disorders (AUD) cause significant morbidity and mortality worldwide, but pharmacological treatments for them are underused, despite evidence of efficacy. Acamprosate, naltrexone, nalmefene and disulfiram are all approved in one or more region for the treatment of AUD. Baclofen currently has a temporary indication in France. Safety considerations for using psychopharmacological treatments in this patient group include the impact of concurrent alcohol consumption at high levels; multiple physical comorbidities that may interfere with pharmacological effects, distribution and metabolism; and concomitant medication for the treatment of comorbid physical and psychiatric conditions. The five drugs, including an extended-release injectable suspension of naltrexone, have different safety profiles that need to be balanced with the treatment objective (initiation or continuation of abstinence, or reduction of drinking), individual patient preferences and comorbid conditions. Appropriate treatment will be based on the unique risk–benefit profile in each case.
Drug-Induced Mitochondrial Toxicity
Iain P. Hargreaves, Mesfer Al Shahrani, Luke Wainwright, Simon J. R. Heales

ABSTRACT
The mitochondrial respiratory chain (MRC) and ATP synthase (complex V) play an essential role in cellular energy production by the process of oxidative phosphorylation. In addition to inborn errors of metabolism, as well as secondary causes from disease pathophysiology, an impairment of oxidative phosphorylation can result from drug toxicity. These ‘off-target’ pharmacological effects can occur from a direct inhibition of MRC enzyme activity, an induction of mitochondrial oxidative stress, an uncoupling of oxidative phosphorylation, an impairment of mitochondrial membrane structure or a disruption in the replication of mitochondrial DNA. The purpose of this review is to focus on the off-target mitochondrial toxicity associated with both commonly used pharmacotherapies and a topical ‘weight loss’ agent. The mechanisms of drug-induced mitochondrial impairment will be discussed together with putative therapeutic strategies to counteract the adverse effects of the pharmacotherapy.

Drug-Induced QT/QTc Interval Shortening: Lessons from Drug-Induced QT/QTc Prolongation
Marek Malik

ABSTRACT
The review discusses safety implications of drugs found to shorten the QT/QTc interval. It uses parallels with drug-induced QT/QTc prolongation. It summarizes the evidence that increases in repolarization heterogeneity are likely more important for arrhythmia induction and maintenance than the absolute changes in the QT/QTc duration. The review further compares the direct evidence of proarhythmia caused by QT-prolonging and -shortening drugs. At present, there is little proof of QT-shortening drugs causing ventricular fibrillation in more than rare isolated instances. Comparisons of the incidence of the congenital syndromes show that short QT syndrome is much rarer than long QT syndrome, similar to the findings of short QT intervals compared with long QT intervals in the general population. Nevertheless, potential concerns come from experimental drugs developed to increase the current of potassium-rectifying channels. Some of these drugs were found to cause ventricular fibrillation in isolated hearts. Still, population exposure to drug-induced QT shortening is likely substantially lower compared with QT prolongation, especially if considering that most of the processes that decrease the so-called repolarization reserve are associated with QT prolongation. Finally, the review lists reasons why purely theoretical concepts of pharmaceutical risk cannot be used to develop regulatory guidance and concludes that at present, no additional tests and/or general acceptance restrictions are needed for the approval of QT-shortening drugs.
**ABSTRACT**

**Introduction:** Metoclopramide is recommended for adults with breakthrough or refractory chemotherapy-induced nausea and vomiting (CINV) and for CINV prophylaxis in children. The drug regulatory agencies of Canada and the EU have revised the labelling of metoclopramide to contraindicate its use in children aged <1 year and to caution against its use in children aged <5 years and its duration of use beyond 5 days.

**Objective:** This review describes the safety of metoclopramide in children when given for any indication.

**Methods:** We conducted electronic searches in MEDLINE and Embase as of 9 March 2015. All studies in English reporting adverse effects associated with the use of metoclopramide in children (aged ≤18 years) were included. Adverse effects that had a cumulative incidence of at least 1% and were reported in prospective studies were synthesized.

**Results:** A total of 108 (57 prospective) studies involving 2699 patients (2745 metoclopramide courses) were included. The most common adverse effects reported in prospective studies of metoclopramide in children were extrapyramidal symptoms (EPS; 9%, 95% confidence interval [CI] 5–17), diarrhea (6%, 95% CI 4–9), and sedation (multiple-dose studies: 6%, 95% CI 3–12). Dysrhythmia, respiratory distress/arrest, neuroleptic malignant syndrome, and tardive dyskinesia were rarely associated with metoclopramide use.

**Limitations:** The definitions of adverse effects reported in the included studies were heterogeneous, and the risk of bias in most studies was moderate.

**Conclusions:** The most commonly reported adverse effects associated with the use of metoclopramide in children—EPS, diarrhea, and sedation—were reversible and of no long-term significance. Adverse effects that were life threatening or slow to resolve were rarely associated with its use in children.
Signal of Gastrointestinal Congenital Malformations with Antipsychotics After Minimising Competition Bias: A Disproportionality Analysis Using Data from Vigibase®

François Montastruc, Francesco Salvo, Mickaël Arnaud, Bernard Bégaud

ABSTRACT

Introduction: Investigations have highlighted the lack of evidence regarding the likelihood of congenital malformations following exposure to antipsychotic drugs during pregnancy. To gain further knowledge regarding their safety, we evaluated signals of congenital malformations with antipsychotics using Vigibase®, the World Health Organization (WHO) Global Individual Case Safety Report (ICSR) database.

Method: A case/non-case study was conducted in Vigibase® between 1967 and 2014. Signals of disproportionate reporting (SDRs) were detected using the proportional reporting ratio (PRR), which defines SDRs as drug-report associations with a PRR ≥2, Chi square ≥4, and number of cases ≥3. SDR detection for antipsychotics was performed for congenital malformations after removing all reports related to drug competitors and reports of movement disorders from the database.

Results: After removing reports related to drug competitors (antiepileptics, antidepressants, antivirals) and movement disorders, three signals were revealed: ‘palate disorders congenital’ (PRR 2.1, 95 % CI 1.6–2.9, Chi square = 30; n = 41), ‘oesophageal disorders congenital’ (PRR 2.5, 95 % CI 1.3–4.7, Chi square = 11; n = 10) and ‘anorectal disorders congenital’ (PRR 3.0, 95 % CI 1.6–5.6, Chi square = 13; n = 11). Among antipsychotics, phenothiazines with a piperazine side-chain, risperidone and aripiprazole appeared to be more suspect.

Conclusion: Confirming a first signal from spontaneous reporting data, three SDRs for antipsychotics and gastrointestinal congenital abnormalities were unmasked in Vigibase®. This signal should be further explored by ad hoc pharmacoepidemiologic studies in order to assess whether it is relevant for prescription and public health.
ABSTRACT

Introduction: A translational bioinformatics challenge exists in connecting population and individual clinical phenotypes in various formats to biological mechanisms. The Medical Dictionary for Regulatory Activities (MedDRA®) is the default dictionary for adverse event (AE) reporting in the US Food and Drug Administration Adverse Event Reporting System (FAERS). The ontology of adverse events (OAE) represents AEs as pathological processes occurring after drug exposures.

Objectives: The aim of this work was to establish a semantic framework to link biological mechanisms to phenotypes of AEs by combining OAE with MedDRA® in FAERS data analysis. We investigated the AEs associated with tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) targeting tyrosine kinases. The five selected TKIs/mAbs (i.e., dasatinib, imatinib, lapatinib, cetuximab, and trastuzumab) are known to induce impaired ventricular function (non-QT) cardiotoxicity.

Results: Statistical analysis of FAERS data identified 1053 distinct MedDRA® terms significantly associated with TKIs/mAbs, where 884 did not have corresponding OAE terms. We manually annotated these terms, added them to OAE by the standard OAE development strategy, and mapped them to MedDRA®. The data integration to provide insights into molecular mechanisms of drug-associated AEs was performed by including linkages in OAE for all related AE terms to MedDRA® and the existing ontologies, including the human phenotype ontology (HP), Uber anatomy ontology (UBERON), and gene ontology (GO). Sixteen AEs were shared by all five TKIs/mAbs, and each of 17 cardiotoxicity AEs was associated with at least one TKI/mAb. As an example, we analyzed “cardiac failure” using the relations established in OAE with other ontologies and demonstrated that one of the biological processes associated with cardiac failure maps to the genes associated with heart contraction.

Conclusion: By expanding the existing OAE ontological design, our TKI use case demonstrated that the combination of OAE and MedDRA® provides a semantic framework to link clinical phenotypes of adverse drug events to biological mechanisms.

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Ethical and Practical Considerations in Removing Black Box Warnings from Drug Labels

James S. Yeh, Ameet Sarpatwari, Aaron S. Kesselheim

ABSTRACT

Boxed warnings—also known as “black box” warnings—can be a powerful tool in communicating drug risks to physicians and patients. The overall number of boxed warnings has grown in recent years as the US Food and Drug Administration (FDA) has approved more drugs on the basis of limited pre-marketing information and as new safety issues for marketed drugs have been identified. Two recent manufacturers’ petitions to remove boxed warnings on the drugs rosiglitazone (Avandia) and varenicline (Chantix) have led to divergent FDA decisions and revealed different considerations involved in boxed warning imposition and removal. For ethical and practical reasons, the FDA is justified in applying a higher standard for boxed warning removal than for imposition, as removal of a boxed warning may have unintended effects on physician and patient behavior. However, no guidelines on boxed warning removal currently exist. To promote safe use of approved prescription drugs, the FDA should adopt a uniform and transparent process governing decisions to impose or remove boxed warnings.
Contemporary Reflections on the Safety of Long-Term Aspirin Treatment for the Secondary Prevention of Cardiovascular Disease

Alexander C. Fanaroff, Matthew T. Roe

ABSTRACT

Aspirin has been the cornerstone of therapy for the secondary prevention treatment of patients with cardiovascular disease since landmark trials were completed in the late 1970s and early 1980s that demonstrated the efficacy of aspirin for reducing the risk of ischemic events. Notwithstanding the consistent benefits demonstrated with aspirin for both acute and chronic cardiovascular disease, there are a number of toxicities associated with aspirin that have been showcased by recent long-term clinical trials that have included an aspirin monotherapy arm. As an inhibitor of cyclooxygenase (COX), aspirin impairs gastric mucosal protective mechanisms. Previous trials have shown that up to 15–20% of patients developed gastrointestinal symptoms with aspirin monotherapy, and approximately 1% of patients per year had a clinically significant bleeding event, including 1 in 1000 patients who suffered an intracranial or fatal bleed. These risks have been shown to be compounded for patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI) who are also treated with other antithrombotic agents during the acute care/procedural period, as well as for an extended time period afterwards. Given observations of substantial increases in bleeding rates from many prior long-term clinical trials that have evaluated aspirin together with other oral platelet inhibitors or oral anticoagulants, the focus of contemporary research has pivoted towards tailored antithrombotic regimens that attempt to either shorten the duration of exposure to aspirin or replace aspirin with an alternative antithrombotic agent. While these shifts are occurring, the safety profile of aspirin when used for the secondary prevention treatment of patients with established cardiovascular disease deserves further consideration.

Diagnosis and Management of Drug-Induced Liver Injury (DILI) in Patients with Pre-Existing Liver Disease

Rolf Teschke, Gaby Danan

ABSTRACT

The relationship between drugs and pre-existing liver disease is complex, particularly when increased liver tests (LTs) or new symptoms emerge in patients with pre-existing liver disease during drug therapy. This requires two strategies to assess whether these changes are due to drug-induced liver injury (DILI) as a new event or due to flares of the underlying liver disease. Lacking a valid diagnostic biomarker, DILI is a diagnosis of exclusion and requires causality assessment by RUCAM, the Roussel Uclaf Causality Assessment Method, to establish an individual causality grading of the suspected drug(s). Flares of pre-existing liver disease can reliably be assessed in some hepatotropic virus infections by polymerase chain reaction (PCR) and antibody titers at the beginning and in the clinical course to ascertain flares during the natural course of the disease. Unfortunately, flares cannot be verified in many other liver diseases such as alcoholic liver disease, since specific tests are unavailable. However, such a diagnostic approach using RUCAM applied to suspected DILI cases includes clinical and biological markers of pre-existing liver diseases and would determine whether drugs or underlying liver diseases caused the LT abnormalities or the new symptoms. More importantly, a clear diagnosis is essential to ensure effective disease management by drug cessation or specific treatment of the flare up due to the underlying disease.
Age at First Rotavirus Vaccination and Risk of Intussusception in Infants: A Public Health Modeling Analysis
Chee Fu Yung, Chia Yin Chong, Koh Cheng Thoon

ABSTRACT

Introduction: The epidemiology of naturally occurring intussusception is known to increase significantly between the ages of 3 and 8 months. Post-licensure studies have reported a fivefold and twofold increase in intussusception in the first week after the first dose and second dose, respectively, of current rotavirus vaccines (RVs).

Purpose: We carried out a public health risk analysis to model the impact of age at first vaccination in relation to rotavirus vaccination and risk of intussusception in infants.

Method: We created a static model for a birth cohort followed until 1 year old to estimate the number of excess intussusception hospitalizations which could be caused by three different infant rotavirus vaccination schedules. A relative risk of 5.45 in the first 7 days after the first dose and 1.75 in the first 7 days after the second dose was used in the model.

Result: We estimated that the risk of intussusception would be the lowest at about 1 in 49,000 if both first and second dose RVs were given at <3 months of age followed by 1 in 41,000 if first dose RVs were given at <3 months and second dose RVs were given at 3–5 months. It would be highest at about 1 in 11,000 if infants received both doses when >3 months old.

Conclusion: Our epidemiological example illustrates the importance of ensuring that the first two doses of RVs are administered in infants <3 months old whenever possible to minimize the risk of intussusception as an adverse event following rotavirus vaccination.

Risk of Liver Injury Associated with Green Tea Extract in SLIMQUICK® Weight Loss Products: Results from the DILIN Prospective Study
Elizabeth X. Zheng, Simona Rossi, Robert J. Fontana, Raj Vuppalanchi

ABSTRACT

Introduction: Herbal and dietary supplements (HDS) have been increasingly recognized as a cause for acute liver injury (Navarro et al. Hepatology 60(4):1399–1408, 2014; Bailey et al. J Nutr 141:261–266, 2011). HDS products frequently contain numerous ingredients, and are marketed under various product names. A perusal of marketed weight loss products indicates that green tea extract (GTE) is a common ingredient in many. We aimed to describe the course and outcome of six patients who developed liver injury attributed to SLIMQUICK® weight loss products.

Methods: Patients with suspected drug-induced liver injury were enrolled in a prospective study of the Drug-Induced Liver Injury Network (DILIN) and causality was assessed by a panel of hepatologists. During the period under study, 6 of 1091 cases of liver injury were attributed to a SLIMQUICK® product and were assigned causality scores of probable, highly likely, or definite.

Results: Six cases of acute liver injury attributed to SLIMQUICK® products were enrolled in the DILIN prospective study between 2007 and 2011. All were women aged 22 to 58 years. Two had a normal body weight and four were mildly obese (body mass index 22.9–32.2 kg/m2). All were taking SLIMQUICK® products for weight loss and no patient reported prior use. Laboratory tests revealed a hepatocellular pattern of injury, with initial alanine aminotransferase (ALT) levels above 1000 U/L in all but one patient. Three patients were hospitalized and one underwent successful liver transplantation.

Conclusions: SLIMQUICK® products can lead to severe acute hepatocellular liver injury, which may result in transplantation. Given the frequency of GTE as a component in weight loss products, this ingredient should be studied further as a possible cause for liver injury.
ABSTRACT

Introduction: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA), and is being investigated for the treatment of psoriasis. Both conditions can present in women of child-bearing potential, but pregnancy was exclusion and discontinuation criterion in tofacitinib randomized controlled trials (RCTs) because of the unknown effects of tofacitinib on mother and child. Tofacitinib is a small molecule that has the potential to cross the placenta.

Objective: The objective was to report outcomes of pregnancy cases identified through April 2014 from tofacitinib RA/psoriasis RCTs, RA post-approval non-interventional studies, and spontaneous adverse-event reporting.

Methods: Pregnancy outcomes were categorized as follows: healthy newborn, medical termination, fetal death, congenital malformation, spontaneous abortion, or pending/lost to follow-up.

Results: Out of 9815 patients, 1821 female patients of child-bearing age were enrolled in the RA/psoriasis RCTs; 47 women became pregnant, including 33 who received tofacitinib monotherapy, 13 who received combination therapy with methotrexate (RA patients only), and one patient whose therapy was still blinded. No fetal deaths were reported. One congenital pulmonary valve stenosis (monotherapy, n = 1), seven spontaneous abortions (monotherapy, n = 4; combination therapy, n = 3), and eight medical terminations (monotherapy, n = 4; combination therapy, n = 3; blinded therapy, n = 1) were identified. Remaining cases reported healthy newborns (n = 25) or were pending/lost to follow-up (n = 6). Forty-four cases of paternal exposure to tofacitinib were reported (monotherapy, n = 43; combination therapy, n = 1), including five spontaneous abortions (monotherapy, n = 4; combination therapy, n = 1), 23 healthy newborns, and 16 pending/lost to follow-up.

Conclusions: The pregnancy outcomes reported in this small number of RA/psoriasis patients appear similar to those observed in the general population and in patients treated with biologic therapies for inflammatory diseases. However, definitive conclusions cannot be drawn, and pregnancy outcomes in patients receiving tofacitinib will continue to be monitored.
**Artesunate/Amodiaquine-Induced Acute Extrapyramidal Reactions in Children and Younger Adults: Case Series Assessment**

Mulugeta Russom, Dawit Tesfai, Semere Gebregiorgis, Abdulmumini Usman

**ABSTRACT**

**Introduction:** Several studies conducted in African countries reported the artesunate and amodiaquine (AS/AQ) tablet as a safe and well-tolerated anti-malarial drug in children and younger adults. The aim of this case series assessment was to assess the causal relationship between the AS/AQ tablet and extrapyramidal reactions in children and younger adults and to investigate the factor(s) predisposing to the adverse drug reactions.

**Methods:** The causal relationship of all the cases was first assessed individually using the Naranjo Probability Scale and then subjected to a case series assessment using Austin Bradford–Hill criteria.

**Results:** A total of 43 acute extrapyramidal reactions associated with the AS/AQ tablet were reported between 2012 and 16 November, 2015 to the Eritrean Pharmacovigilance Centre. The causality was found to be probable or highly probable for 33 (76.7 %) of the cases and the rest (10; 23.3 %) of the cases had a possible causal association. The extrapyramidal reactions had more or less similar clinical features in most of the cases and were characterized by abnormal involuntary contractions of muscles. The median age and body weight of the cases were 15 years and 40 kg, respectively, and 70 % of them were males. 90.7% of the reactions manifested in children and younger adults (aged <26 years). In most of the cases, reactions manifested in the third day from the start of treatment and 88.3 % of cases were hospitalized.

**Conclusion:** The causal relationship between the AS/AQ tablet and extrapyramidal reactions in children and younger adults was found to be apparent and possibly owing to dose accumulation or an overdose of amodiaquine.
The Impact of Experiencing Adverse Drug Reactions on the Patient’s Quality of Life: A Retrospective Cross-Sectional Study in the Netherlands
Leàn Rolfes, Florence van Hunsel, Katja Taxis, Eugène van Puijenbroek

ABSTRACT

Introduction: There is little information as to what extent adverse drug reactions (ADRs) influence patients’ health-related quality of life (HR-QOL). From a pharmacovigilance perspective, capturing and making the best use of this information remains a challenge. The Netherlands Pharmacovigilance Centre Lareb received about 1800 reports after the packaging of the drug Thyrax® (levothyroxine; Aspen Pharma Trading Limited, Dublin, Ireland) changed from a brown glass bottle to a blister package in the Netherlands.

Objective: The objective of this study was to explore the impact of ADRs on HR-QOL in patients who reported a possible ADR to Lareb in relation to the change in the packaging of the drug Thyrax®.

Methods: Patients who reported an ADR in relation to the Thyrax® packaging change were included in this study. A web-based adapted version of the COOP/WONCA questionnaire was sent to explore the HR-QOL before versus during the ADR, expressed on a 5-point scale from no impact (1) to high impact (5). Multivariable linear regression analysis was used to identify factors correlated with change in HR-QOL.

Results: Overall, 1167 patients returned the questionnaire (71.2 % response rate). The difference in HR-QOL was −0.8 for physical, −1.2 for mental, −1.4 for daily activities, −1.3 for social, and −1.3 for overall health status (p < 0.001 for each domain). Age, sex, educational level of the patient, and absence from work due to an ADR were correlated with at least one domain, while severity of the ADR was found to be correlated with all domains of HR-QOL.

Conclusion: Patients who reported possible ADRs after the Thyrax® packaging change experienced a significant decrease in HR-QOL. This impact was highest for the domains ‘daily activities’, ‘overall health status’, and ‘mental health’ and lowest for ‘physical fitness’. 


The Patient’s Voice in Pharmacovigilance: Pragmatic Approaches to Building a Patient-Centric Drug Safety Organization
Meredith Y. Smith, Isma Benattia

ABSTRACT

Patient-centeredness has become an acknowledged hallmark of not only high-quality health care but also high-quality drug development. Biopharmaceutical companies are actively seeking to be more patient-centric in drug research and development by involving patients in identifying target disease conditions, participating in the design of, and recruitment for, clinical trials, and disseminating study results. Drug safety departments within the biopharmaceutical industry are at a similar inflection point. Rising rates of per capita prescription drug use underscore the importance of having robust pharmacovigilance systems in place to detect and assess adverse drug reactions (ADRs). At the same time, the practice of pharmacovigilance is being transformed by a host of recent regulatory guidances and related initiatives which emphasize the importance of the patient’s perspective in drug safety. Collectively, these initiatives impact the full range of activities that fall within the remit of pharmacovigilance, including ADR reporting, signal detection and evaluation, risk management, medication error assessment, benefit–risk assessment and risk communication. Examples include the fact that manufacturing authorization holders are now expected to monitor all digital sources under their control for potential reports of ADRs, and the emergence of new methods for collecting, analysing and reporting patient-generated ADR reports for signal detection and evaluation purposes.
Benefit–Risk Assessment of Fish Oil in Preventing Cardiovascular Disease

Bill Lands

ABSTRACT

Cardiovascular disease (CVD) is a preventable disease, which combines two general processes: chronic vascular inflammation and acute thrombosis. Both are amplified with positive feedback signals by n-6 eicosanoids derived from food-based n-6 highly unsaturated fatty acids (n-6 HUFA). This amplification is lessened by competing actions of n-3 HUFA. Death results from fatal interactions of the vascular wall with platelets and clotting proteins. The benefits of fish oil interventions are confounded by complex details in pharmacokinetics, pharmacodynamics, adverse events, timescale factors, topology, financial incentives and people’s sense of cause and effect. Two basic aspects of n-3 HUFA that are overlooked in CVD dynamics are saturable, hyperbolic responses of the enzymes continually supplying n-6 HUFA and hard-to-control positive feedback receptor signals by excessive n-6 HUFA–based mediators. Multiple feedback loops in inflammation and thrombosis have diverse mediators, and reducing one mediator that occurs above its rate-limiting levels may not reduce the pathophysiology. Clinicians have developed some successful interventions that decrease CVD deaths in the form of secondary prevention. However, the current high CVD prevalence in the USA remains unchanged, and successful primary prevention of CVD remains uncertain. This review weighs the available evidence to help clinicians, the biomedical community and the public put the use of fish oil supplements into a balanced perspective.

Drug-Induced Liver Injury: Highlights from a Review of the 2015 Literature

Philip Sarges, Joshua M Steinberg, James H Lewis

ABSTRACT

Numerous publications contributed to the expanding knowledge base about drug-induced liver injury (DILI) in 2015. New findings from the US Drug Induced Liver Injury Network (DILIN) in their most recently updated registry include a 1- to 3-week delay in the appearance of acute DILI from short-course antibiotics such as cefazolin. They corroborated the finding that acute DILI in patients with underlying liver disease was far more severe and potentially fatal than in patients without liver disease. The only drug that seemed to have an increased risk of hepatotoxicity in these patients was azithromycin. While nearly one in six patients with acute DILI had persistently elevated liver tests at 6 months, and results for 75 % of these patients continued to be abnormal at 12 months, most of these “chronic” injury cases were relatively minor and the result of cholestatic hepatotoxins. Newly described DILI agents include tolvaptan, as well as some new direct-acting antiviral protease inhibitors for chronic hepatitis C. The latter have been associated with serious acute hepatitis, hyperbilirubinemia, and decompensation. Herbal hepatotoxicity continues to be increasingly reported, although applying causality assessment to these cases can, in fact, be more challenging than with prescription drugs. As important as cases with DILI, the class of PCSK9 inhibitors used to lower low-density lipoprotein (LDL) cholesterol have not been associated with significant liver injury, in contrast with other lipid-lowering agents. With respect to pharmacologic DILI risk factors, new data show that drugs metabolized by cytochrome P450 enzymes had a nearly four times higher likelihood of causing DILI. Interestingly, high lipophilia, which was previously felt to be a risk factor for DILI, was not found to be associated, although more study is needed to confirm this observation. While human leukocyte antigen (HLA) genotypes have been linked to several specific agents, the role of such testing in the general population remains undefined due to the currently low positive and negative predictive values of the available tests. New DILI biomarkers, specifically microRNA-122 and keratin-18, among others, appear to have the necessary predictive value to determine the prognosis and outcome of patients with paracetamol (acetaminophen [AAP])-induced acute liver failure (ALF), and may be of great benefit in deciding who requires N-acetylcysteine (NAC), and for what duration. Treatment options for other forms of DILI remain limited; no firm conclusions can currently be drawn for the use of NAC in non-AAP ALF.
Benefit and Risk of Tofacitinib in the Treatment of Rheumatoid Arthritis: A Focus on Herpes Zoster

Kunihiro Yamaoka

ABSTRACT

The biologics have revolutionized the treatment of rheumatoid arthritis (RA). However, there are still patients that are difficult to control and a cure is still not achievable. Tofacitinib, a Janus kinase (JAK) inhibitor is an orally available, new-in-class, disease-modifying anti-rheumatic drug with similar efficacy to biologics. JAK is activated by multiple cytokines involved in the pathology of RA, and affects non-immune and immune cells, mainly the lymphocytes. Besides its anti-rheumatic effect, the recent focus has been on adverse events. As with other biologics, serious infections have been observed especially with patients with lymphopenia, consistent with the mechanism of action. The major difference in adverse events from other disease-modifying anti-rheumatic drugs is the prominent increase in the occurrence of herpes zoster; it is increased worldwide, especially in Asia. There are other concerns such as malignancies and hyperlipidemia that may cause cardiovascular events that deserve further attention.

Drug Interactions of Direct-Acting Oral Anticoagulants

John Leonard Fitzgerald, Laurence Guy Howes

ABSTRACT

In recent years, new direct-acting oral anticoagulants (DOACs) have been introduced into clinical practice that specifically inhibit either factor Ia or Xa. These drugs have, to a large extent, replaced warfarin for the treatment of venous thrombosis, pulmonary embolism, and non-valvular atrial fibrillation. They have potential advantages over warfarin in providing more stable anticoagulation and the lack of a need for regular venesection to monitor activity. They also have the promise of less drug and food interactions. All of these drugs are substrates for the permeability glycoprotein (P-gp) excretion system, and several are metabolised, in part, by cytochrome P450 (CYP) 3A4. This current article assesses the interactions that do or may occur with the DOACs, particularly with respect to the P-gp and CYP3A4 systems.

Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries: A Review of Prevalence and Contributing Factors

Mulugeta Tarekegn Angamo, Leanne Chalmers, Colin M. Curtain

ABSTRACT

Adverse drug reactions (ADRs) are one of the leading causes of hospital admissions and morbidity in developed countries and represent a substantial burden on healthcare delivery systems. However, there is little data available from low- and middle-income countries. This review compares the prevalence and characteristics of ADR-related hospitalisations in adults in developed and developing countries, including the mortality, severity and preventability associated with these events, commonly implicated drugs and contributing factors. A literature search was conducted via PubMed, Scopus, Web of Science, Embase, ProQuest and Google Scholar to find articles published in English from 2000 to 2015. Relevant observational studies were included. The median (with interquartile range [IQR]) prevalence of ADR-related hospitalisation in developed and developing countries was 6.3 % (3.3–11.0) and 5.5 % (1.1–16.9), respectively. The median proportions of preventable ADRs in developed and developing countries were 71.7 % (62.3–80.0) and 59.6 % (51.5–79.6), respectively. Similarly, the median proportions of ADRs resulting in mortality in developed and developing countries were 1.7 % (0.7–4.8) and 1.8 % (0.8–8.0), respectively. Commonly implicated drugs in both settings were antithrombotic, non-steroidal anti-inflammatory and cardiovascular drugs. Older age, female gender, number of medications, renal impairment and heart failure were reported to be associated with an increased risk for ADR-related hospitalisation in both settings while HIV/AIDS was implicated in developing countries only.
ABSTRACT

**Introduction:** Active surveillance pharmacovigilance is a systematic approach to medicine safety assessment and health systems strengthening, but has not been widely implemented in low- and middle-income countries. This study aimed to assess the cost effectiveness of a national active surveillance pharmacovigilance system for highly active antiretroviral therapy (HAART) compared with the existing spontaneous reporting system in Namibia.

**Methods:** A cost–utility analysis from a governmental perspective compared active surveillance pharmacovigilance to spontaneous reporting. Data from a sentinel site active surveillance program in Namibia from August 2012 to April 2013 was projected to all HIV-infected adults initiating HAART in Namibia. Costs (pharmacovigilance program, HAART, adverse event [AE] treatment), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs, dollars/QALY) were evaluated. Analysis was completed for (i) cohort analysis: a single cohort beginning HAART in 1 year in Namibia followed over their remaining lifetime, and (ii) population analysis: patients continued to enter and leave care and treatment over 10 years.

**Results:** For the cohort analysis, totals were US$21,267,902 (2015 US dollars) and 116,224 QALYs for care and treatment under active surveillance pharmacovigilance versus US$15,257,381 and 116,122 QALYs for care and treatment under spontaneous reporting pharmacovigilance, resulting in an ICER of US$58,867/QALY for active surveillance compared with spontaneous reporting pharmacovigilance. The population analysis ICER was US$4989/QALY. Results were sensitive to quality of life associated with AEs.

**Conclusion:** Active surveillance pharmacovigilance was projected to be highly cost effective to improve treatment for HIV in Namibia. Active surveillance pharmacovigilance may be valuable to improve lives of HIV patients and more efficiently allocate health resources in Namibia.
Drug Safety Monitoring in Children: Performance of Signal Detection Algorithms and Impact of Age Stratification

Osemeke U. Osokogu, Caitlin Dodd, Alexandra Pacurariu, Florentia Kaguelidou

ABSTRACT

Introduction: Spontaneous reports of suspected adverse drug reactions (ADRs) can be analyzed to yield additional drug safety evidence for the pediatric population. Signal detection algorithms (SDAs) are required for these analyses; however, the performance of SDAs in the pediatric population specifically is unknown. We tested the performance of two SDAs on pediatric data from the US FDA Adverse Event Reporting System (FAERS) and investigated the impact of age stratification and age adjustment on the performance of SDAs.

Methods: We tested the performance of two established SDAs: the proportional reporting ratio (PRR) and the empirical Bayes geometric mean (EBGM) on a pediatric dataset from FAERS (2004–2012). We compared the performance of the SDAs with a published pediatric-specific reference set by calculating diagnostic test-related statistics, including the area under the curve (AUC) of receiver operating characteristics. Impact of age stratification and age-adjustment on the performance of the SDAs was assessed. Age adjustment was performed by pooling (Mantel-Hanszel) stratum-specific estimates.

Results: A total of 115,674 pediatric reports (patients aged 0–18 years) comprising 893,587 drug-event combinations (DECs) were analysed. Crude values of the AUC were similar for both SDAs: 0.731 (PRR) and 0.745 (EBGM). Stratification unmasked four DECs, e.g., ‘ibuprofen and thrombocytopenia’. Age adjustment did not improve performance.

Conclusion: The performance of the two tested SDAs was similar in the pediatric population. Age adjustment does not improve performance and is therefore not recommended to be performed routinely. Stratification can reveal new associations, and therefore is recommended when either drug use is age-specific or when an age-specific risk is suspected.


Patient-Reported Safety Information: A Renaissance of Pharmacovigilance?

Linda Hämark, June Raine, Hubert Leufkens, I. Ralph Edwards, Ugo Moretti

ABSTRACT

The role of patients as key contributors in pharmacovigilance was acknowledged in the new EU pharmacovigilance legislation. This contains several efforts to increase the involvement of the general public, including making patient adverse drug reaction (ADR) reporting systems mandatory. Three years have passed since the legislation was introduced and the key question is: does pharmacovigilance yet make optimal use of patient-reported safety information? Independent research has shown beyond doubt that patients make an important contribution to pharmacovigilance signal detection. Patient reports provide first-hand information about the suspected ADR and the circumstances under which it occurred, including medication errors, quality failures, and ‘near misses’. Patient-reported safety information leads to a better understanding of the patient’s experiences of the ADR. Patients are better at explaining the nature, personal significance and consequences of ADRs than healthcare professionals’ reports on similar associations and they give more detailed information regarding quality of life including psychological effects and effects on everyday tasks. Current methods used in pharmacovigilance need to optimise use of the information reported from patients. To make the most of information from patients, the systems we use for collecting, coding and recording patient-reported information and the methodologies applied for signal detection and assessment need to be further developed, such as a patient-specific form, development of a severity grading and evolution of the database structure and the signal detection methods applied. It is time for a renaissance of pharmacovigilance.
ABSTRACT

Many Pacific Island countries (PICs) are recipients of funding support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). However, most of these countries cannot be expected to meet Global Fund and World Health Organization (WHO) minimum requirements for a functioning pharmacovigilance (PV) system. We argue that a different approach is required to move PV forward in such countries. Although the long-term aim is to build adequate national PV capacity, we propose an approach in which resources are focused initially towards ensuring a proper system for the reporting of “problems with medicines” such as substandard and counterfeit products. The limited health system resources in these countries require that PV will be supported by some of the organizations also giving funding aid for the supply of medicines.

Causality Assessment in Premarketing Drug Clinical Trials: Regulatory Evolution in the USA and Ongoing Concerns

Stephen A. Goldman

ABSTRACT

Since 1993, how to assess the causality of serious adverse events in premarking drug clinical trials has undergone sustained regulatory evolution in the USA. In that year, an investigational drug study for chronic hepatitis B virus infection was emergently stopped after a patient suddenly exhibited hepatic failure and lactic acidosis, which later developed, along with pancreatitis and peripheral neuropathy, in several others after drug discontinuation. Five patients eventually died, including three despite emergency liver transplantation. The drug’s multisystem toxicity was not predicted by preclinical animal studies, with grave injury to human mitochondria subsequently implicated. A concerned US Food and Drug Administration (FDA) created a task force whose findings would have a lasting impact on the agency’s thinking. In 1994, the FDA proposed to amend its investigational new drug reporting requirements largely based on task force recommendations for ways to enhance the likelihood that sponsors and investigators would consider investigational agents as a possible cause of serious adverse events mimicking the underlying disease or concomitant drug toxicity. Then, in its 1997 final rule for expedited safety reporting requirements for drugs and biologics, the FDA advised sponsors that such reporting of serious, unexpected clinical trial cases would be expected when “there is a reasonable suspected causal relationship between the investigational product and the adverse event (i.e., the causal relationship cannot be ruled out).” This last clause was codified into the suspected adverse drug reaction definition in the FDA’s 2003 safety reporting requirements for drugs and biologics proposed rule. The negatively received suspected adverse drug reaction and proposed causality standard were not adopted in the FDA’s 2010 finalized investigational new drug safety reporting regulations, the agency stating that “‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event.” However, such new requirements as aggregate analysis of specific events and expedited reporting of animal or in vitro data suggesting significant harm to humans, and subsequent guidance that sponsors develop “a systematic approach” to premarking safety assessment, are among the components of the FDA’s efforts to enhance determination of a “reasonable possibility” of causality. They are also philosophically consistent with the 1993 task force recommendations, and a reminder of the inherent hazards associated with the use of investigational drugs, particularly in the early stages of human study.
ABSTRACT

Exposure to drugs during pregnancy has the potential to harm offspring. Teratogenic effects are the most feared adverse outcomes in newborns; however, a wide spectrum of less known, usually reversible and often acute, neonatal adverse events can also occur due to drug intake by mothers during pregnancy, particularly in close proximity to delivery. This narrative review is aimed at the description of drugs and drug classes for which licit maternal use in the predelivery period has been associated with neonatal non-teratogenic disorders. For each drug class, epidemiology, clinical features, biological mechanism and management of these adverse reactions have been discussed in detail. Although these adverse reactions have been described mainly for substances used illicitly for recreational purposes, several prescription drugs have also been involved; these include mainly psychotropic medications such as opioids, antidepressants, antiepileptics and antipsychotics. These effects can be partly explained by withdrawal syndromes (defined also as ‘neonatal abstinence syndrome’) caused by the delivery-related discontinuation of the drug disposition from the mother to the fetus, with symptoms that may include feeding disorders, tremors, irritability, hypotonia/hypertonia, vomiting and persistent crying, occurring a few hours to 1 month after delivery. Otherwise, neonatal neurological and behavioral effects can also be caused by a residual pharmacological effect due to an accumulation of the drug in the blood and tissues of the newborn, with various symptoms related to the toxic effects of the specific drug class, usually developing a few hours after birth. With few exceptions, validated protocols for the assessment and management of withdrawal or residual pharmacological effects of these drugs in neonates are often lacking or incomplete. Spontaneous reporting of these adverse reactions seems limited, although it might represent a useful tool for improving our knowledge about drug-induced neonatal syndromes.

Hepatic Safety of Atypical Antipsychotics: Current Evidence and Future Directions

Mahmoud Slim, Inmaculada Medina-Caliz, Andres Gonzalez-Jimenez

ABSTRACT

The newer atypical antipsychotic agents (AAPs) represent an attractive therapeutic option for a wide range of psychotic disorders, including schizophrenia and bipolar mania, because of the reduced risk of disabling extrapyramidal symptoms. However, their growing use has raised questions about their tolerability over the endocrine, metabolic, and cardiovascular axes. Indeed, atypical antipsychotic drugs are associated, to differing extents, with mild elevation of aminotransferases related to weight gain, AAP-induced metabolic syndrome, and nonalcoholic fatty liver disease. Although the hepatic safety of new AAPs seems improved over that of chlorpromazine, they can occasionally cause idiosyncratic liver injury with varying phenotypes and, rarely, lead to acute liver failure. However, AAPs are a group of heterogeneous, chemically unrelated compounds with distinct pharmacological and pharmacokinetic properties and substantially different safety profiles, which precludes the notion of a class effect for hepatotoxicity risk and highlights the need for an individualized therapeutic approach. We discuss the current evidence on the hepatotoxicity potential of AAPs, the emerging underlying mechanisms, and the limitations inherent to this group of drugs for both establishing a proper causality assessment and developing strategies for risk management.
Neuropsychiatric Effects of HIV Antiviral Medications
Glenn J. Treisman, Olivia Soudry

ABSTRACT
The development of antiretroviral therapy (ART) has dramatically increased the lifespan of HIV patients but treatment is complicated by numerous adverse effects and toxicities. ART complications include neuropsychiatric, metabolic, gastrointestinal, cardiac, and numerous other toxicities, and clinicians often have to choose one toxicity over another to offer the best medication regimen for a patient. Some antiviral drugs cause significant neuropsychiatric complications, including depression, cognitive impairment, and sleep disturbance. Even in careful studies, it may be difficult to determine which effects are related to the virus, the immune system, or the treatment. Of the six currently marketed classes of antiviral drugs, the nucleoside reverse transcriptase inhibitors and the non-nucleoside reverse transcriptase inhibitors have been most commonly associated with neuropsychiatric complications. Within these classes, certain drugs are more likely to cause difficulty than others. We review the contention regarding the central nervous system (CNS) complications of efavirenz, as well as debate about the role of CNS penetration in drug effectiveness and toxicity. A thorough working knowledge of the neuropsychiatric consequences of ART allows clinicians to tailor treatment more successfully to individual patients as well as to identify ART more quickly as the source of a problem or symptom.

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Targeted Spontaneous Reporting: Assessing Opportunities to Conduct Routine Pharmacovigilance for Antiretroviral Treatment on an International Scale
Beth Rachlis, Rakhi Karwa, Celia Chema, Sonak Pastakia, Sten Olsson

ABSTRACT
Introduction: Targeted spontaneous reporting (TSR) is a pharmacovigilance method that can enhance reporting of adverse drug reactions related to antiretroviral therapy (ART). Minimal data exist on the needs or capacity of facilities to conduct TSR.

Objectives: Using data from the International epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium, the present study had two objectives: (1) to develop a list of facility characteristics that could constitute key assets in the conduct of TSR; (2) to use this list as a starting point to describe the existing capacity of IeDEA-participating facilities to conduct pharmacovigilance through TSR.

Methods: We generated our facility characteristics list using an iterative approach, through a review of relevant World Health Organization (WHO) and Uppsala Monitoring Centre documents focused on pharmacovigilance activities related to HIV and ART and consultation with expert stakeholders. IeDEA facility data were drawn from a 2009/2010 IeDEA site assessment that included reported characteristics of adult and pediatric HIV care programs, including outreach, staffing, laboratory capacity, adverse event monitoring, and non-HIV care.

Results: A total of 137 facilities were included: East Africa (43); Asia–Pacific (28); West Africa (21); Southern Africa (19); Central Africa (12); Caribbean, Central, and South America (7); and North America (7). Key facility characteristics were grouped as follows: outcome ascertainment and follow-up; laboratory monitoring; documentation—sources and management of data; and human resources. Facility characteristics ranged by facility and region. The majority of facilities reported that patients were assigned a unique identification number (n = 114; 83.2 %) and most sites recorded adverse drug reactions (n = 101; 73.7 %), while 82 facilities (59.9 %) reported having an electronic database on site.

Conclusion: We found minimal information is available about facility characteristics that may contribute to pharmacovigilance activities. Our findings, therefore, are a first step that can potentially assist implementers and facility staff to identify opportunities and leverage their existing capacities to incorporate TSR into their routine clinical programs.
Innovative Digital Tools and Surveillance Systems for the Timely Detection of Adverse Events at the Point of Care: A Proof-of-Concept Study
Christian Hoppe, Patrick Obermeier, Susann Muehlhans, Maren Alchikh

ABSTRACT

Introduction and Objective: Regulatory authorities often receive poorly structured safety reports requiring considerable effort to investigate potential adverse events post hoc. Automated question-and-answer systems may help to improve the overall quality of safety information transmitted to pharmacovigilance agencies. This paper explores the use of the VACC-Tool (ViVi Automated Case Classification Tool) 2.0, a mobile application enabling physicians to classify clinical cases according to 14 pre-defined case definitions for neuroinflammatory adverse events (NIAE) and in full compliance with data standards issued by the Clinical Data Interchange Standards Consortium.

Methods: The validation of the VACC-Tool 2.0 (beta-version) was conducted in the context of a unique quality management program for children with suspected NIAE in collaboration with the Robert Koch Institute in Berlin, Germany. The VACC-Tool was used for instant case classification and for longitudinal follow-up throughout the course of hospitalization. Results were compared to International Classification of Diseases, Tenth Revision (ICD-10) codes assigned in the emergency department (ED).

Results: From 07/2013 to 10/2014, a total of 34,368 patients were seen in the ED, and 5243 patients were hospitalized; 243 of these were admitted for suspected NIAE (mean age: 8.5 years), thus participating in the quality management program. Using the VACC-Tool in the ED, 209 cases were classified successfully, 69% of which had been missed or miscoded in the ED reports. Longitudinal follow-up with the VACC-Tool identified additional NIAE.

Conclusion: Mobile applications are taking data standards to the point of care, enabling clinicians to ascertain potential adverse events in the ED setting and during inpatient follow-up. Compliance with Clinical Data Interchange Standards Consortium (CDISC) data standards facilitates data interoperability according to regulatory requirements.

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National ADR Monitoring System in China
Yongfang Hou, Xinling Li, Guizhi Wu, Xiaofei Ye

ABSTRACT

It has been more than 25 years since an adverse drug reaction (ADR) monitoring agency was first established in China. In the past few years, the National ADR Monitoring System (NADRMS) has developed rapidly in the country. However, this system has not been reviewed in detail in the literature. Our aim was to demonstrate how individual case safety reports (ICSRs) are reported and evaluated and how data quality control is achieved in China. We also aimed to discuss the present status and future of NADRMS. We reviewed the relevant regulations and literature around ADR reporting in China. ADR report collection tools in China have gone through three phases, namely paper-based reporting, software-based reporting using standalone computers, and online reporting. Nowadays the online reporting system plays an important role in China and the number of ADR reports has rapidly increased. NADRMS is similar to most of the ADR reporting systems around the world, but also has its own unique characteristics such as four levels of monitoring agencies. In summary, there is still a long way to go for China to establish a high-level ADR monitoring system to ensure drug safety.
Drug–Drug Interactions, Effectiveness, and Safety of Hormonal Contraceptives in Women Living with HIV

Kimberly K. Scarsi, Kristin M. Darin, Catherine A. Chappell

ABSTRACT

It has been more than 25 years since an adverse drug reaction (ADR) monitoring agency was first established in China. In the past few years, the National ADR Monitoring System (NADRMS) has developed rapidly in the country. However, this system has not been reviewed in detail in the literature. Our aim was to demonstrate how individual case safety reports (ICSRs) are reported and evaluated and how data quality control is achieved in China. We also aimed to discuss the present status and future of NADRMS. We reviewed the relevant regulations and literature around ADR reporting in China. ADR report collection tools in China have gone through three phases, namely paper-based reporting, software-based reporting using standalone computers, and online reporting. Nowadays the online reporting system plays an important role in China and the number of ADR reports has rapidly increased. NADRMS is similar to most of the ADR reporting systems around the world, but also has its own unique characteristics such as four levels of monitoring agencies. In summary, there is still a long way to go for China to establish a high-level ADR monitoring system to ensure drug safety.

Tyrosine Kinase Inhibitor-Induced Interstitial Lung Disease: Clinical Features, Diagnostic Challenges, and Therapeutic Dilemmas

Rashmi R. Shah

ABSTRACT

Since the approval of the first molecularly targeted tyrosine kinase inhibitor (TKI), imatinib, in 2001, TKIs have heralded a new era in the treatment of many cancers. Among their innumerable adverse effects, interstitial lung disease (ILD) is one of the most serious, presenting most frequently with dyspnea, cough, fever, and hypoxemia, and often treated with steroids. Of the 28 currently approved TKIs, 16 (57%) are reported to induce ILD with varying frequency and/or severity. The interval from drug administration to onset of ILD varies between patients and between TKIs, with no predictable time course. Its incidence is variously reported to be approximately 1.6–4.3% in Japanese populations and 0.3–1.0% in non-Japanese populations. The mortality rate is in the range of 20–50%. Available evidence (primarily following the use of erlotinib and gefitinib in Japan because of the unique susceptibility of that population) has identified a number of susceptibility and prognostic risk factors (male sex, a history of smoking, and pre-existing pulmonary fibrosis being the main ones). Although the precise mechanism is not understood, collective evidence suggests that immune factors may be involved. If TKI-induced ILD is confirmed by thorough evaluation of the patient and exclusion of other causes, management is supportive, and includes discontinuation of the culprit TKI and administration of steroids. Discontinuing the culprit TKI presents a clinical dilemma because the diagnosis of TKI-induced ILD in a patient with pre-existing pulmonary fibrosis can be challenging, the patient may have TKI-responsive cancer with no suitable alternative, and switching to an alternative agent, even if available, carries the risk of the patient experiencing other toxic effects. Preliminary evidence suggests that therapy with the culprit TKI may be continued under steroid cover and/or at a reduced dose. However, this approach requires careful individualized risk–benefit analysis and further clinical experience.
ABSTRACT

Introduction: Clinical trials have identified peripheral oedema (PO) as an adverse event of vildagliptin (an oral anti-diabetic drug [OAD]). A post-marketing study (PMS) was conducted to advance the understanding of vildagliptin use and particular safety concerns identified within the risk-management plan. PMS objectives included comparing the hazards between vildagliptin monotherapy and combination therapy for selected a priori identified risks, including PO.

Aim: This study was a per-protocol supplementary analysis to investigate the pattern of onset and effect of vildagliptin combination therapy on PO risk.

Methods: The PMS used an observational cohort design. OAD exposure, selected risk factors and outcome data were collected from general practitioners in England regarding vildagliptin users for the 6-month period after starting treatment. Data analysis comprised univariate case/non-case analysis, time-to-onset analysis and Cox proportional hazard models to estimate hazard ratios (HR) of PO adjusting for selected patients’ baseline characteristics.

Results: The study cohort included 4828 patients (median age 63 years; interquartile range [IQR] 54–71), 2692 of whom were male (55.8 %). The crude cumulative hazard of PO was 19.09 cases (95 % confidence interval [CI] 13.54–26.10) per 1000 person-years; 50 % of cases occurred during the first 34 days of treatment. A significantly faster time to PO onset was observed in patients prescribed concomitant sulfonylureas versus other treatment combinations (log rank test [LRT] p = 0.0365); in patients with a prior history of PO (LRT p < 0.001), arrhythmia (LRT p = 0.0003) or hypertension (LRT p = 0.0125); and in patients aged ≥60 years (LRT p = 0.0047). Similarly, the case/non-case univariate analysis indicated that patients with PO were older; had a higher prevalence of a history of either arrhythmia, hypertension or PO; and frequently used a sulfonylurea in combination. In the hazard function analysis, only sex and prior PO history had a profound effect on risk of PO after starting vildagliptin. Furthermore, effect modification was observed between sex and prior PO history; in male patients of average age (62 years), the HR was 12.84 (95 % CI 4.96–33.23); in females, it was 1.44 (95 % CI 0.32–6.40).

Conclusions: In this planned supplementary analysis, the findings suggest that PO occurred most frequently within 1 month after starting treatment with vildagliptin, and previous PO history and male sex in elderly patients were important predictors of this risk. The observation that concomitant use of a sulfonylurea may also increase PO risk early after starting treatment should be taken into consideration if prescribing OADs in combination with vildagliptin.
ABSTRACT

Introduction: Patient reporting of adverse drug reactions (ADRs) to spontaneous reporting systems can make a valuable contribution to pharmacovigilance. However, the implementation and promotion of patient reporting systems (PRSs) differ worldwide.

Objective: The objective of the study was to describe attitudes toward PRSs, and progress toward implementing such systems among national competent authorities participating in the World Health Organization Programme for International Drug Monitoring.

Methods: A web-based questionnaire was constructed based on qualitative interviews, and distributed through SurveyMonkey® to all countries listed on the World Health Organization Programme for International Drug Monitoring (n = 178) during November and December of 2015. Data were analyzed using descriptive statistics and Chi-square tests.

Results: A total of 143 valid questionnaires were received from 141 countries (79.2 %). A spontaneous reporting system for both healthcare professionals and patients was present in 58 countries (41.1 %). An official PRS to report ADRs directly was implemented in 44 countries (31.2 %) and in a pilot stage in five countries (3.5 %). Patients were not allowed to report in 34 countries (24.1 %). The reasons for not having an official PRS were mainly a lack of resources/budget (56.5 %) or a lack of information/education for patients (56.5 %). When analyzing the attitudes among the respondents toward a PRS, most acknowledge that the general public contributes to the detection or strength of drug safety signals (82.2 % agree or strongly agree) and with information that is not present in healthcare professional reports (80.7 % agree or strongly agree). For respondents, giving feedback to patients could be an incentive for patients to report more (80.8 % agree or strongly agree). To be able to further PRSs, guidelines on promoting a PRS efficiently to the general public (87.4 % agree or strongly agree), training courses/conferences (86.7 % agree or strongly agree), or a public list of Lareb’s scientific publications (86.7 % agree or strongly agree) were the support measures most well accepted by the respondents.

Conclusions: Most countries accept ADR reports from patients by an official reporting system designed for patients or through the existing system for healthcare professionals. The main reasons for not having a PRS is financial restraints and a lack of information/education of patients. Attitudes toward a PRS are positive, but some countries fear that they will not be able to handle an increase in reports.
ABSTRACT

Introduction: The under-reporting of adverse drug events (ADEs) is an international health concern. A number of studies have assessed the root causes but, to our knowledge, little information exists relating under-reporting to practices and systems used for the recording and tracking of drug-related adverse event observations in ambulatory settings, institutional settings, and retail pharmacies.

Objectives: Our objective was to explore the process for reporting ADEs in US hospitals, ambulatory settings, and retail pharmacies; to explore gaps and inconsistencies in the reporting process; and to identify the causes of under-reporting ADEs in these settings.

Methods: The Tufts Center for the Study of Drug Development (Tufts CSDD) interviewed 11 thought leaders and conducted a survey between May and August 2014 among US-based healthcare providers (HCPs) in diverse settings to assess their experiences with, and processes for, reporting ADEs.

Results: A total of 123 individuals completed the survey (42 % were pharmacists; 27 % were nurses; 15 % were physicians; and 16 % were classified as ‘other’). HCPs indicated that the main reasons for under-reporting were difficulty in determining the cause of the ADE, given that most patients receive multiple therapies simultaneously (66 % of respondents); that HCPs lack sufficient time to report ADEs (63 % of respondents); poor integration of ADE-reporting systems (53 % of respondents); and uncertainty about reporting procedures (52 % of respondents).

Discussion: The results of this pilot study identify that key factors contributing to the under-reporting of ADEs relate to a lack of standardized process, a lack of training and education, and a lack of integrated health information technologies.
Prevention of Medication Errors in Hospitalized Patients: The Japan Adverse Drug Events Study  
Chihiro Noguchi, Mio Sakuma, Yoshinori Ohta, David W. Bates

ABSTRACT

Introduction: The nature of medication errors (MEs) and the frequency of identified or intercepted MEs are not being scrutinized in daily practice in Japan.

Objectives: The aim of this study was to clarify the epidemiology of MEs and the risk factors for non-intercepted and unidentified MEs.

Methods: The Japan Adverse Drug Events (JADE) study was a prospective cohort study carried out at three tertiary-care teaching hospitals in Japan. Participants were consecutive patients (N = 3459) aged ≥15 years who were admitted to the study wards. MEs were identified by on-site reviews of all medical charts, self-reports, and prescription queries by pharmacists. Two independent physicians reviewed and classified all MEs and adverse drug events and determined the stages at which the MEs occurred and whether there was interception or identification of the MEs.

Results: A total of 514 MEs were observed among 433 patients. Sixty-four percent of MEs occurred at the ordering stage. Among these, 60% were due to duplicate drug orders. Overall, 63% and 45% of MEs were not intercepted or identified during hospitalization, respectively. The independent risk factors for non-intercepted MEs were hospitalization in the surgical ward (odds ratio [OR] 2.94) and the intensive care unit (OR 3.57). MEs by resident physicians were more likely to be intercepted (OR 0.52 for non-intercepted MEs).

Conclusions: MEs frequently occurred and most at the ordering stage. Almost half of MEs were not intercepted or identified. Many MEs at the later stages were less likely to be intercepted and resulted in actual patient harm. Systems to improve the identification and interception of MEs should be implemented.
Association between the Occurrence of Adverse Drug Events and Modification of First-Line Highly Active Antiretroviral Therapy in Ghanaian HIV Patients
Raymond A. Tetteh, Edmund T. Nar Hay, Margaret Lartey

ABSTRACT

Introduction: Patients initiated on highly active antiretroviral therapy (HAART) generally remain on medication indefinitely. A modification in the HAART regimen may become necessary because of possible acute or chronic toxicities, concomitant clinical conditions, development of virological failure or the advent of adverse drug events. The study documents adverse drug events of HIV-positive Ghanaian patients with HAART modifications. It also investigates the association between documented adverse drug events and HAART modification using an unmatched case–control study design.

Method: The study was conducted in the Fevers Unit of the Korle Bu Teaching Hospital and involved patients who attended the HIV Care Clinic between January 2004 and December 2009. Data from 298 modified therapy patients (cases) were compared with 298 continuing therapy patients (controls) who had been on treatment for at least 1 month before the end of study. Controls were sampled from the same database of a cohort of HIV-positive patients on HAART, at the time a case occurred, in terms of treatment initiation ±1 month. Data were obtained from patients’ clinical folders and the HIV clinic database linked to the pharmacy database. The nature of the documented adverse drug events of the cases was described and the association between the documented adverse drug events and HAART modification was determined by logistic regression with reported odds ratios (ORs) and their 95% confidence interval (CI).

Results: Among the 298 modified therapy patients sampled in this study, 52.7% of them had at least one documented adverse drug event. The most documented adverse drug event was anaemia, recorded in 18.5% of modified therapy patients, all of whom were on a zidovudine-based regimen. The presence of documented adverse drug events was significantly associated with HAART modification [adjusted OR = 2.71 (95% CI 2.11–3.48), p < 0.001].

Conclusion: Among HIV patients on HAART, adverse drug events play a major role in treatment modification. Occurrence of adverse drug events may be used as a predictor for possible therapy modification. We recommend the institution of active pharmacovigilance in HIV treatment programmes as it permits the proper identification and characterisation of drug-related adverse events. This can help develop approaches towards their management and also justify therapy modifications.
Treatment-Related Progressive Multifocal Leukoencephalopathy in Multiple Sclerosis: A Comprehensive Review of Current Evidence and Future Needs
Emanuele D’Amico, Aurora Zanghi, Carmela Leone, Hayrettin Tumani

ABSTRACT
Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic infection of the central nervous system caused by the John Cunningham virus (JCV) that has been associated with therapeutic immunosuppression in patients with multiple sclerosis (MS). So far, more than 600 cases of PML have been reported in association with natalizumab administration. There have also been confirmed cases of PML in individuals who received fingolimod and dimethyl fumarate without previous natalizumab treatment. The new licensed disease-modifying therapies for MS carry the risk of immunosuppressant and so of JCV reactivation. Various factors have been identified with increased risk of developing PML, including a positive JCV serology, natalizumab administration for >2 years, and prior use of immunosuppressive agents. Clinicians can employ such tools for patients’ risk stratification, but the incidence of PML among patients receiving natalizumab therapy has not changed. In this review we outline the current state of understanding of PML pathogenesis and patients’ risk stratification. The landscape of MS is dramatically changing and knowledge of the side effects of the licensed therapies is imperative to enable optimal decision making.

Risk–Benefit Profile of Direct-Acting Oral Anticoaguants in Established Therapeutic Indications: An Overview of Systematic Reviews and Observational Studies
Emanuel Raschi, Matteo Bianchin, Walter Ageno, Roberto De Ponti

ABSTRACT
Since 2008, the direct-acting oral anticoagulants (DOACs) have expanded the therapeutic options of cardiovascular diseases with recognized clinical and epidemiological impact, such as non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE), and also in the preventive setting of orthopedic surgical patients. The large body of evidence, not only from pivotal clinical trials but also from ‘real-world’ postmarketing observational findings (e.g. analytical epidemiological studies and registry data) gathered to date allow for a first attempt at verifying a posteriori whether or not the pharmacological advantages of the DOACs actually translate into therapeutic innovation, with relevant implications for clinicians, regulators and patients. This review aims to synthesize the risk–benefit profile of DOACs in the aforementioned consolidated indications through an ‘evidence summary’ approach gathering the existent evidence-based data, particularly systematic reviews with meta-analyses of randomized controlled trials, as well as observational studies, comparing DOACs with vitamin K antagonists. Clinical evidence will be discussed and compared with major international guidelines to identify whether an update is needed. Controversial clinically relevant safety issues will be also examined in order to highlight current challenges and unsettled questions (e.g. actual bleeding risk in susceptible populations). It is anticipated that the large number of publications on NVAF or VTE (44 systematic reviews with meta-analyses and 12 observational studies retained in our analysis) suggests the potential existence of overlapping studies and calls for common criteria to qualitatively and quantitatively assess discordances, thus guiding future research.
ABSTRACT

Introduction: Spontaneous reporting of adverse drug reactions (ADRs) remains the cornerstone of postmarketing drug safety surveillance (pharmacovigilance); however, one of its main limitations is incomplete data, thus limiting conclusions about causality assessment.

Objective: The primary aim of this study was to assess the completeness of ADR reports sent by general practitioners (GPs) to regional pharmacovigilance centres and the secondary objective was to identify factors associated with complete ADR reports.

Methods: All ADR reports sent by GPs to the Midi-Pyrénées Regional Pharmacovigilance Center (Toulouse, France) from 1 January 2010 to 31 December 2013 were reviewed. Healthcare professionals and patients can forward an ADR using either an online form through the Pharmacology Information Bulletin website (http://www.bip31.fr) or ‘traditional’ ADR reports (i.e. email, letter or fax). According to information provided in ADR reports (i.e. patient identification, ADR, date of occurrence, clinical description, drugs, etc.), reports were classified into three groups: ‘well-documented’, ‘slightly documented’ or ‘poorly documented’. A multivariate logistic regression was performed to investigate potential factors associated with a ‘well-documented’ ADR report.

Results: During the study period, 613 ADR reports were analysed. Among these reports, only 12.7 % were classified as ‘well-documented’, 68.5 % as ‘slightly documented’ and 18.8 % as ‘poorly documented’. An association between a ‘well-documented’ ADR report and its ‘seriousness’ was found (odds ratio = 1.70 [95 % CI 1.04–2.76], p = 0.01). No association between report completeness (‘well-documented’ report) and GP practice location or mode of ADR reporting was found.

Conclusions: The study shows that only one out of eight ADR reports from GPs was ‘well-documented’. Therefore, it appears to be important to promote further information being available regarding the data required in ADR reports to optimise the evaluation of drug causality.
Vaccine Case–Population: A New Method for Vaccine Safety Surveillance
Hélène Théophile, Nicholas Moore, Philip Robinson, Bernard Bégaud

ABSTRACT

Introduction: The case–population approach compares exposure among cases to that of their source population. By using aggregated data to estimate the denominator, this approach can provide a real-time estimate of an association that could be particularly valuable to explore urgent vaccine safety concerns and to generate signals during a vaccine campaign.

Objective: Our objective was to present the vaccine case–population method, a method derived from the case–population approach and adapted for vaccine safety surveillance, and to test it using several published examples.

Methods: For the vaccine case–population method, exposure in the population is estimated from the sum of at-risk periods using the number of vaccinated individuals, or data of vaccine sales, and the at-risk period considered for the vaccine–event pair. The vaccine case–population method was applied to data from published case–control studies retrieved from the MEDLINE database and having quantified risks associated with vaccines. Odds ratios derived from the vaccine case–population method were compared with those from published case–control studies.

Results: A total of 20 vaccine–event pairs were retrieved in which the vaccine case–population method could be applied. For all identified vaccine–event pairs, when a significant association was found using the vaccine case–population method, a significant association was also found in the corresponding case–control study. Conversely, when no association was found by the vaccine case–population method, no association was found in the corresponding case–control study.

Conclusion: These results suggest that the vaccine case–population method can produce coherent conclusions and may be used in the future for prospective investigation of urgent vaccine safety concerns or for the prospective generation of vaccine safety signals. This method could also be used to identify selection bias from cases excluded from the case–control study.
Estimating Herbal Product Authentication and Adulteration in India Using a Vouchered, DNA-Based Biological Reference Material Library

Dhivya Shanmughanandhan, Subramanyam Ragupathy, Steven G. Newmaster

ABSTRACT

Introduction: India is considered the ‘medicinal garden’ of the world, with 8000 medicinal plants of which 960 are commercial species that are traded nationally and globally. Although scientific studies estimate herbal product adulteration as 42–66% in North America, India does not have any published marketplace studies and subsequent estimates of adulteration in an industry facing considerable supply demands.

Objectives: The goal of this project is to provide an initial assessment of herbal product authentication and adulteration in the marketplace in India by (1) developing a biological reference material (BRM) herbal DNA library for Indian herbal species using DNA barcode regions (ITS2 and rbcL) in order to facilitate accurate species resolution when testing the herbal products; and (2) assessing herbal product identification using our BRM library; and (3) comparing the use of our BRM library to identify herbal products with that of GenBank.

Methods: A BRM herbal DNA library consisting of 187 herbal species was prepared to authenticate the herbal products within India. Ninety-three herbal products representing ten different companies were procured from local stores located at Coimbatore, India. These samples were subjected to blind testing for authenticity using the DNA barcode regions rbcL and ITS2.

Results: The results indicate that 40% of the products tested are authentic, and 60% of the products may be adulterated (i.e. contained species of plants not listed on the product labels). The adulterated samples included contamination (50%), substitution (10%) and fillers (6%). Our BRM library provided a 100% Basic Local Alignment Search Tool (BLAST) match for all species, whereas the GenBank match was 64%.

Conclusions: Our findings suggest that most Indian herbal medicinal products are essentially mixed with one or a few other herbs that could lessen the therapeutic activity of the main ingredients. We do not recommend the use of GenBank to identify herbal products because the use of this non-curated and/or vouchered database will result in inaccurate species identification. These DNA-based tools provide a scientific foundation for herbal pharmacovigilance to ensure the safety and efficacy of natural drugs. This study provides curated BRMs that will underpin innovations in molecular diagnostic biotechnology, which will soon provide more robust estimates of adulteration and commercial tools that will strengthen due diligence in quality assurance within the herbal industry.
ABSTRACT

Introduction: The Bhutan National Pharmacovigilance Centre (NPC) became an official member of the WHO Programme for International Drug Monitoring in December 2014; however, the number of adverse drug reactions (ADRs) reported is very low (50 reports per 773,722 inhabitants over 10 years). Surveys of healthcare professionals (HCPs) in similar countries have indicated that adequate knowledge of both ADRs and ADR reporting is likely to increase the number of ADR reports submitted.

Objective: The aim of this study was to investigate the level of knowledge of both ADRs and ADR reporting among HCPs, including traditional medicine practitioners.

Methods: A cross-sectional survey was conducted, using a validated self-administered questionnaire. The questionnaires were distributed to 670 HCPs, including clinical doctors, nurses, pharmacists and traditional medicine practitioners from four referral hospitals. The survey consisted of 12 questions pertaining to ADRs and 10 questions pertaining to knowledge of ADR reporting. The collected response was then analysed descriptively and results presented as mean ± standard deviation (SD) using SPSS version 20.

Results: The overall response rate was 434 (65 %) questionnaires, with HCPs consisting of clinical doctors (94, 22 %), nurses (257, 59 %), pharmacists (52, 12 %) and traditional medicine practitioners (31, 7 %). The overall mean ± SD score with regard to the level of knowledge of ADRs was 6.52 ± 2.81 out of a maximum score of 12, among which clinical doctors scored 7.48 ± 2.95, nurses 6.15 ± 2.47, pharmacists 8.15 ± 2.49 and traditional medicine practitioners 4.13 ± 3.18. The mean ± SD score with regard to the level of knowledge of ADR reporting among HCPs was 3.94 ± 1.89 out of a maximum score of 10, among which clinical doctors scored 3.93 ± 1.81, nurses 3.75 ± 1.74, pharmacists 5.00 ± 1.81 and traditional medicine practitioners 4.00 ± 1.77.

Conclusion: Clinical doctors and pharmacists have better knowledge of ADRs than nurses and traditional medicine practitioners, while knowledge of ADR reporting was low for all HCPs surveyed.