Forums

1 FDA Introducing Electronic Submission of IND Safety Reports

The US Food and Drug Administration (FDA) is introducing electronic submission of safety reports for investigational new drug (IND) applications through the FDA’s Adverse Event Reporting System (FAERS). The FDA has released new draft guidance on the process as well as supporting technical specification documents. The changes will enable the FDA to review pre- and post-marketing safety data within in the same system, with the same data standard.

Publication of the draft guidance and technical documents should assist drug manufacturers in beginning preparations for when final draft guidance is issued and becomes effective. IND safety reports will be submitted in a reporting format that is consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2B guidelines. The FDA will shortly announce when sponsors can begin voluntary submissions of IND safety reports to FAERS.

“The FDA highly encourages sponsors of all INDs, both commercial and noncommercial, to begin submitting IND safety reports to FAERS voluntarily as soon as the new submission process is available,” said Dr. Janet Woodcock, Director of the FDA’s Center for Drug Evaluation and Research (CDER). IND safety reporting via FAERS will be voluntary until 2 years after the final guidance has been issued, after which it will become mandatory for commercial INDs.

The FDA has created a separate submission path to FAERS for IND safety report submissions; they will remain designated as investigational and will not be publicly available.

US Food and Drug Administration. Digital submission of adverse event reports for investigational new drug applications reflects FDA’s ongoing modernization efforts. 29 Oct 2019. https://www.fda.gov/news-events/press-announcements/digital-submission-adverse-event-reports-investigational-new-drug-applications-reflects-fdas-ongoing. Accessed 11 Dec 2019.

2 Institute for Safe Medication Practices Joins ECRI Institute

The US Institute for Safe Medication Practices (ISMP) and the ECRI Institute have announced that they have formed an agreement to work together to enhance patient safety with regard to medicines, medical devices and healthcare practices. ISMP will become a subsidiary of the ECRI Institute on 2 January 2020, and together the two non-profit organisations will create one of the largest patient safety entities in the world.

Approximately 80% of US hospitals rely on data and recommendations from the ECRI Institute to protect patients from unsafe practices and ineffective products, while the ISMP’s efforts to improve safety in patients have resulted in changes to clinical practice and public policy, including improvements in drug labelling, packaging, preparation and administration.

“This agreement will strengthen our critical contributions to medication safety,” said ISMP President Michael Cohen, “It allows both organizations to retain their core missions while immediately extending our ability to share lifesaving information and further a vision where safe, high-quality healthcare is more readily available”.

“For both organizations, this agreement furthers the mission, deepens expertise, and broadens relationships. It’s a good move for both of us and for all of the organizations we serve, and ultimately for the patients worldwide,” commented ECRI Institute President and CEO Marcus Schabacker.

Institute for Safe Medication Practices. ECRI Institute and Institute for Safe Medication Practices join forces to enhance patient safety. 13 Nov 2019. https://www.ismp.org/news/ecri-institute-and-institute-safe-medication-practices-join-forces-enhance-patient-safety. Accessed 11 Dec 2019.
3 US FDA Enhancing Postmarketing Drug Safety Surveillance

The US FDA has published a draft document on best postmarketing drug safety surveillance practices, says Dr. Janet Woodcock, Director of the CDER, in an FDA statement.

The FDA evaluates over two million adverse event reports annually that are submitted to FAERS through the MedWatch Program, and to the Vaccine Adverse Event Reporting System (VAERS) by patients or their families or healthcare providers, as well as adverse event reports submitted by pharmaceutical companies, and this information is used by the FDA’s Office of Surveillance and Epidemiology, and the Center for Biologics Evaluation and Research’s Office of Biostatistics and Epidemiology, to identify safety concerns and recommend actions to improve safety.

The Cures Act was introduced in 2016 to amend the Federal Food, Drug, and Cosmetic Act by eliminating the requirement for the FDA to prepare a summary analysis of reports of adverse drug reactions (ADRs) received up to 18 months after drug approval or after use of the drug by 10,000 patients.

A new requirement of the Cures Act was for the FDA to make its best practices for drug safety surveillance publicly available on the web. The FDA has now announced the availability of a draft document entitled “Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff”, which outlines the agency’s approach to timely postmarketing analyses of drugs and biologics, and “includes a high-level overview of tools, methods, and signal detection and evaluation activities, using varied data sources, for drug safety surveillance to provide a broader context and a general overview of our overarching effort and commitment in this area”, says Woodcock.

The FDA is constantly seeking new methods for improving its surveillance practices, and is inviting the public to comment on its draft document on postmarketing surveillance.

The regulatory agency has developed a set of posters targeted at both healthcare professionals and consumers, which will be released over a 4-year transition period.

One of these posters is a quick reference guide for healthcare professionals entitled “Your medicine, your knowledge—Improved medicine labels”, which highlights “some of the key medicine labelling changes that are important for consumers”, noted the TGA.

In addition, another three posters have been developed for consumers to raise their awareness of the labelling improvements, and are intended to be displayed in waiting rooms or public areas.

The TGA noted that “medicine labels are already starting to change” and that some of the key information that consumers should be aware of will include the following:

- prominence of active ingredients;
- clearer medicine information, which may include a “Critical Health Information table” that will provide information in a consistent order and will be easy to recognise;
- information on declarable substances (e.g. allergens) will now be required on the medicine label;
- easier dispensing of medicines from pharmacies;
- updated names for Australian medicine ingredients to align with names used internationally.

The TGA highlighted that medicine sponsors will have 4 years (i.e. until 31 August 2020) to implement these changes and fully comply with the new labelling rules. During this transition period, the agency will release targeted communications to consumers regarding the labelling changes.

Therapeutic Goods Administration. Labelling changes: information for health professionals. 18 Oct 2019. https://www.tga.gov.au/labelling-changes-information-health-professionals. Accessed 11 Dec 2019.

5 Drug Approval in EU Should Require Agreement on Fair Price

Experts speaking at the European Public Health Alliance’s Universal Access and Affordable Medicines forum in November 2019 urged that drug approval in the EU should require the pharmaceutical company’s agreement on a fair price, said Elisabeth Mahase in the BMJ.

At the forum, experts across the EU discussed the need for improved transparency from drug companies to enable fairer drug pricing.

“We need a change in law. After European Medicines Agency (EMA) registration, we need to identify what is
a fair price as a basis for negotiation”, commented Carin Uyl-de Groot, Director of the Institute for Medical Technology Assessment at Erasmus University, Rotterdam, the Netherlands. She said that the marketing authorisation process should include assessments of cost effectiveness and fair pricing by the EMA or another organisation after drug effectiveness and safety have been reviewed, and countries could use the fair pricing assessment as a basis for price negotiations with drug companies.

Experts also discussed the need for more research on cancer drugs before their approval, to ensure their effectiveness and to identify the specific patient population which will benefit from treatment with them.

“Only 20–30% of cancer drugs actually have an impact. We make drugs available at a very high speed, without actually knowing how to use them”, said Denis Lacombe, Director General at the European Organisation for Research and Treatment of Cancer. He called for more research into the optimal way to use cancer drugs, and said that they should be less expensive if this information is not available.

Mahase E. EU drug approval should include price evaluation, says expert panel. BMJ. 2019;367:i6591.

6 NICE International Division Open for Business

In response to increasing overseas enquiries, the National Institute for Health and Care Excellence (NICE) is relaunching its International division to advise organisations, ministries and government agencies from outside the UK on health related, evidence-based decision making.

The not-for-profit International division, operating on a fee for service basis, draws on the expertise of internal staff, academic partners and world-wide experts to provide support with cost effective, transparent resource allocation, improved quality of care and equitable access. Clients can attend knowledge transfer seminars in the UK, overseas or via web conference, or employ the consultancy service for more intensive support with technical and institutional training including implementing new methods and programmes, and adapting NICE guidelines to local healthcare settings.

Chief Executive at NICE, Andrew Dillon said “We’re delighted to be relaunching NICE International so that we can share what we’ve learnt over the last 20 years to help other international health and care systems optimise their use of evidence-based practice”.

National Institute for Health and Care Excellence. NICE International returns to deal with growing overseas enquiries. 5 Nov 2019. https://www.nice.org.uk/news/article/nice-international-returns-to-deal-with-growing-oversse-enquiries. Accessed 11 Dec 2019.

7 Concerns About High Cost of Market Exclusivity Extensions

Market exclusivity extensions to promote antibiotic drug development may lead to billions of dollars in additional societal spending on prescription drugs, according to a study conducted by researchers from Harvard Medical School in Boston, US.

The researchers estimated the economic impact of the Re-Valuing Anti-Microbial Products (REVAMP) Act introduced in the US House of Representatives in June 2018 with the goal to promote research and development of novel antibiotic drugs, specifically those targeting multi-drug resistant pathogens. The Act offers manufacturers that gain FDA approval for specific novel antibiotics a 12-month transferable market exclusivity extension voucher that could be applied to an existing brand-name drug or sold to another manufacturer.

The analysis identified 10 antibiotics approved by the FDA from 2007 through 2016 that would likely have qualified for an exclusivity voucher, and each antibiotic was matched to the fast-track drug with the highest revenue losing exclusivity within 4 years of the antimicrobial’s approval date. The median annual revenue of these 10 antimicrobials prior to generic entry was estimated at $US249 million. Accounting for a 75% spending reduction after generic entry, the median spending associated with an exclusivity voucher was $187 million. Total spending associated with a 1-year exclusivity extension for all 10 drugs was estimated at $4.5 billion. “Our results raise important concerns about the overall cost of transferable exclusivity vouchers”, conclude the researchers.

Rome BN, Kesselheim AS. Transferrable market exclusivity extensions to promote antibiotic development: an economic analysis. Clin Infect Dis. Epub 20 Oct 2019. http://doi.org/10.1093/cid/ciz1039. Accessed 11 Dec 2019.

8 TECH-VER Verification Checklist for Economic Models

The newly developed TECHnical VERification (TECH-VER) checklist for validating health economic decision-analytical models can help identify causes of model implementation errors and be used as a training and quality control tool for the development of models, say authors of a report published in PharmacoEconomics.

EMBASE and MEDLINE databases were searched up to May 2019 for studies on the credibility, validation and verification of models for health technology assessment (HTA) or
cost-effectiveness analysis. A draft checklist was developed based on findings from studies identified in the literature review, and applied to health economic models which varied with respect to stakeholder developer, purpose and the maturity of clinical evidence. Iterative revision of the checklist was performed and checked after implementation. The checklist then underwent further revision after discussions with other health economists, until the final version of TECH-VER was created.

The TECH-VER requires a model reviewer, a transparent model, input sources, and detailed documentation reporting the concept, implementation, model inputs and results. It includes five domains: input calculations, event-state calculations, result calculations, uncertainty analysis calculations, and overall checks. The reviewer should assess the justifications of methods used in calculations. Verification tests conducted to check the correctness of implementation of these calculations should include (in consecutive order): black-box tests to check that model calculations align with a priori expectations; white-box testing of program code line by line, or cell by cell for crucial calculations if black-box test results are unexpected; and model replication/parallel programming if issues related to unexpected results from black-box tests cannot be resolved through white-box testing.

“The TECH-VER checklist is a comprehensive checklist for the technical verification of decision analytical models, aiming to help identify model implementation errors and their root causes while improving the transparency and efficiency of the verification efforts”, said the authors. “It is the authors’ aim that the TECH-VER checklist transforms itself to an open-source living document, with possible future versions, or ‘bolt-on’ extensions for specific applications with additional ‘fit-for-purpose’ tests, as well as ‘tips and tricks’ and some demonstrative error examples,” they commented.

Buyukkaramikli NC, Rutten-van Mölken MPMH, Severens JL, et al. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics. Epub 8 Nov 2019. https://doi.org/10.1007/s40273-019-00844-y. Accessed 11 Dec 2019.

9 Dosage Adjustment in Patients with Renal Impairment: eGFR vs CrCl

In most cases, dosage adjustments in patients with renal impairment can be effectively determined using their estimated glomerular filtration rate (eGFR). However, the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) notes in a Drug Safety Update that “in some circumstances, the Cockcroft–Gault formula should be used to calculate creatinine clearance (CrCl)”.

The MHRA has received queries about choosing which renal function measurement to use. In some patient groups or clinical situations, eGFR can overestimate renal function, and can lead to prescribing higher than recommended medication doses.

The agency has received reports of ADRs when eGFR was used to determine dosage adjustments in patients with renal impairment. One Yellow Card report involved an elderly patient treated with a direct-acting anticoagulant (DOAC) who developed a significant bleeding event; a review revealed that the dose initiated “was too high for the patient”. A cross-sectional study of 8 drugs in 80 general practices from the UK revealed that in elderly patients with reduced renal function, there was widespread prescribing outside recommendations; using eGFR overestimated renal function for up to 28% of patients.

Using CrCl is recommended for patients in the following situations: ≥ 75 years of age; at extremes of muscle mass; taking DOACs; taking nephrotoxic drugs; or taking drugs which are largely renally excreted and have a narrow therapeutic index. Healthcare professionals are requested to report suspected ADRs via the Yellow Card scheme.

10 Drug Company Gifts to GPs May Influence Prescribing

Gifts from pharmaceutical companies to general practitioners (GPs) in France appears to influence primary care prescribing, according to findings of a retrospective study published in the BMJ.

Data from the National Health Data System database managed by the French National Health Insurance (NHI) system, and from the French Transparency in Healthcare database, were used to investigate the association between the monetary value of drug company gifts to GPs and prescribing patterns of 41,257 GPs who worked in the private sector in France in 2016.

The amount per visit reimbursed by the NHI was significantly lower in GPs for whom no gifts were reported in the Transparency in Healthcare database than in those who received at least one drug company gift valued at ≥ €1000 in 2016 (− €5.33; p < 0.001).

GPs who received no gifts more frequently prescribed generic antibacterials, antihypertensives and HMG-CoA reductase inhibitors (statins) than GPs who received gifts.
valued at ≥ €1000 (all p < 0.001). They significantly less frequently prescribed vasodilators but significantly more often prescribed ACE inhibitors versus ACE inhibitors plus angiotensin-II receptor antagonists (sartans) compared with GPs who received gifts valued at ≥ €1000. There were no significant differences in prescribing of aspirin or generic antidepressants or proton pump inhibitors between GPs with and without gifts from drug companies.

“Our study shows that gifts to GPs are common and associated with less rational drug prescriptions for patients and more expenses for the National Health Insurance”, said the authors. The findings “suggest that French GPs who do not receive gifts from pharmaceutical companies have better drug prescription efficiency indicators (as defined by France’s National Healthcare Insurance) and less costly drug prescriptions than those who receive gifts”, they concluded.

Goupil B, Balusson F, Naudet F, et al. Association between prescriptions than those who receive gifts”, they concluded.

11 Vaccine Safety Monitoring in Australia

In Australia, adverse events in vaccinated patients are monitored by the AusVaxSafety system, notes the Department of Health, and a report of safety during 2018 indicated that vaccines in the National Immunisation Program (NIP) are very safe.

Vaccine recipients or their carer are sent an SMS message by the 290 participating immunisation clinics, asking whether the recipient had any postvaccination adverse events. Responses include Yes, No, or Stop (to opt out). During 2018, > 80,000 SMS messages were sent, with > 58,000 responses.

A short survey is sent to Yes responders, requesting a description of the adverse event. Report of a visit to the emergency department (ED) or a physician is flagged with the provider, who follows up with the recipient and notifies the TGA division if required. Responses are closely monitored by AusVaxSafety, enabling potential problems to be detected and acted on.

Children are vaccinated against serious diseases at the schedule points of 2, 4, 6, 12 and 18 months of age and at 4 years. NIP modifications from July 2018 include the third dose of pneumococcal vaccine at 12 months rather than 6 months of age, and Hib vaccine at 18 months of age and a quadrivalent meningococcal vaccine at 12 months of age rather than a combined Hib-meningococcal vaccine at 12 months of age. An adverse event was reported by 9%, 12%, 7%, 12%, 13% and 19% of patients at the 2, 4, 6, 12 and 18 months and 4 years schedule points, respectively. An ED or physician visit was reported by 0.9%, 0.9%, 0.7%, 1.2%, 1.6% and 2% of patients. The most frequently reported adverse events were fever, irritability, and injection site pain, swelling or redness, which are similar to reports in previous years. The proportion of serious adverse events (SAEs) was unaltered, and the overall type and proportion of adverse events was similar before and after modification of the NIP schedule.

Adolescents are vaccinated against human papillomavirus and diphtheria/tetanus/whooping cough. Adverse events were reported by 9% of patients, with 0.6% requiring an ED or physician visit. The most commonly reported events were tiredness and injection site pain.

Pregnant women are vaccinated against influenza and diphtheria/tetanus/whooping cough. Adverse events were reported by 6% of patients, with 0.3% requiring an ED or physician visit. The most commonly reported events were injection site pain, swelling or redness.

Department of Health—Australia. Vaccine safety in Australia. AusVaxSafety summary report 2018. 18 Nov 2019. https://www.health.gov.au/sites/default/files/documents/2019/11/vaccine-safety-in-australia-ausvaxsafety-summary-report-2018.pdf. Accessed 11 Dec 2019.

12 ASCO’s Decision Aid: Improved Adverse Event Attribution

Results of a preliminary study, reported in the Journal of Oncology Practice, show that use of the Decision Aid developed by the American Society of Clinical Oncology (ASCO) improves the accuracy of reporters in the attribution of SAEs to a drug, but has no apparent effect on determining seriousness.

Under US FDA regulations, sponsors of clinical trials relating to IND applications are required to reports SAEs that are unexpected and suspected to be drug-related. Based on the FDA’s Final Rule and related guidances, ASCO developed the one-page Decision Aid stepwise flowchart. The crossover study included 29 physician-investigators or research staff from community or academic research sites who are involved in SAE reporting decisions at their site. Ten clinical case studies were evaluated, with five assessed with the assistance of the Decision Aid tool.

Compared with an unassisted assessment, the Decision Aid tool did not significantly improve the accuracy of determining serious for the case studies (odds ratio [OR] 0.87; 0.31, 2.46). However, the accuracy of attributing an SAE to the drug was significantly increased (OR 3.60; 1.15, 11.4).
Most participants assessed the tool as being helpful (93%) and allowing improved decision-making time (69%) and confidence in reporting (83%), and indicated that they would use the tool in practice (83%). The preferred delivery method was by mobile application, followed by hard copy/paper or via the ASCO website. Potential barriers to tool use included contract/protocol expectations or restrictions, and variability of the SAE review and decision-making process among sites.

“The Decision Aid shows promise as a method to improve the quality of SAE attribution”, note the authors, “which may improve the detection of valid safety signals and reduce the administrative burden of uninformative investigational new drug safety reports”. They add that “study of the Decision Aid in a larger sample with analysis stratified by participant role and SAE reporting experience would further assess the tool’s impact”.

Mileham KF, Schenkel C, Chuk MK, et al. Assessing an ASCO decision aid for improving the accuracy and attribution of serious adverse event reporting from investigators to sponsors. J Oncol Pract. Epub 24 Oct 2019. http://doi.org/10.1200/JOP.19.00366. Accessed 11 Dec 2019.

13 Overcoming Cancer Drug Cost Forecast Challenges in Canada

The accuracy of forecasting cancer drug costs can be improved by using a hybrid approach combining automated time-series forecasting and expert customisation, report researchers from Canada.

The researchers developed a forecasting framework from both a technical and a policy perspective to provide a flexible tool that can improve the accuracy of forecasts while incorporating multiple forecasts for the Canadian province of Ontario.

The optimal forecasts for the top nine drug policies that made up the first 80% of the total budget in the previous 12 months (‘big budget drivers’ [BBDs]) funded by the Provincial Drug Reimbursement Programs resulted in errors within ±4%. It was estimated that the forecast error from the automated approach for these nine BBD policies would have been approximately $Can2.2 million, compared with approximately $Can7.2 million using a manual approach. This corresponds to savings of $Can5 million for these policies. “The flexibility provided by the hybrid approach should ultimately lead to improved accuracy, which will help achieve our policy-related goal: to help the programme make better decisions regarding to ability to fund drugs in the oncology pipeline”, note the researchers. This approach to drug budget forecasting was implemented in Ontario for the first time in the 2017/2018 fiscal year. The forecasts resulted in a 1% error for the overall budget, corresponding to an overestimate of expenditures by $Can3 million.

Murray PM, Shalaby YA, Ieraci L, et al. Forecasting Ontario oncology drug expenditures: a hybrid approach to improving accuracy. Appl Health Econ Health Policy. Epub 14 Nov 2019. http://doi.org/10.1007/s40258-019-00533-z. Accessed 11 Dec 2019.

14 Restricted Access to CAR-T Cell Therapies due to Uncertainty

Although the high-cost CAR-T cell therapies tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) have been granted reimbursement in several countries in Europe and in USA, restricted access was granted in the UK, France and Germany due to uncertainties in evidence, say authors of a study presented as a poster at the 22nd Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

This study investigated whether the evidence for Kymriah and Yescarta was sufficient for the drugs to be granted reimbursement by HTA bodies in France (Transparency Committee [TC]), Germany (Federal Joint Committee [G-BA]), Sweden (Dental and Pharmaceutical Benefits Agency [TLV]), the UK (NICE) and USA (Institute for Clinical and Economic Review [ICER]), and the association between gaps in evidence and granting of restricted access. Reports from all five HTA bodies for Yescarta for one indication (diffuse large B-cell lymphoma [DLBCL]) and for Kymriah for two indications (acute lymphoblastic leukaemia [ALL] and DLBCL) were assessed.

While ICER considered evidence provided certainty of the cost effectiveness of Yescarta and Kymriah, NICE and the TLV granted access to the drugs despite a high level of uncertainty in their cost effectiveness. Gaps in clinical evidence were identified for both drugs in all five countries, primarily with regard to the lack of long-term data on overall survival and progression-free survival, and a lack of comparative data. NICE, G-BA, TLV and the TC required further evidence to demonstrate the long-term clinical benefit and cost-effectiveness of the drugs.

Strategies have been implemented to mitigate the risk of introducing these high-cost drugs.

“The fact that both Yescarta and Kymriah have widespread access, despite significant uncertainty in clinical evidence and cost-effectiveness (where relevant), is largely reflective of the high unmet need in DLBCL, the willingness of payers to access CAR-T therapies and the high level of innovation perceived”, said the authors. “For both drugs, HTA bodies are recommending that re-assessment occurs
when more clinical and economic data (from clinical trials, country-specific real world evidence and indirect comparisons) becomes available”, they noted.

Thomas M, Craddy P, Foxon G. Was the evidence base for Yescarta and Kymriah sufficient to justify their cost and secure patient access across 5 markets? [abstract no. PDG79]. 22nd Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research. 2-6 Nov 2019; Copenhagen, Denmark. https://www.ispor.org/heor-resources/presentations-database/presentation/euro2019-3121/97788. Accessed 11 Dec 2019.

15 Drug-Induced Intracranial Hypertension

Many drugs used in dermatology appear to be associated with idiopathic intracranial hypertension (IIH), leading to the suggestion that the term drug-induced intracranial hypertension (DIIH) should be introduced, say authors of a systematic review published in the American Journal of Clinical Dermatology.

Investigators searched MEDLINE, EMBASE, and Cochrane Review Databases for all articles reporting potentially drug-related cases of IIH up until June 2019. In total, 235 articles were considered to be relevant. For all cases which met modified Dandy criteria for diagnosis of IIH, the Koh algorithm for adverse drug reactions (ADR) was used to assess the likelihood of IIH being drug-related.

Overall, 259 cases of DIIH were verifiable. Vitamin A (retinol) and its derivatives (isotretinoin and tretinoin) were most frequently associated with DIIH (84 cases). Other drugs or drug classes most strongly associated with DIIH (≥ 20 cases) included recombinant growth hormone and tetracyclines (including doxycycline, minocycline and tetracycline). Lithium was also strongly associated with DIIH (15–19 cases) while corticosteroids were determined to be moderately associated with DIIH (10–14 cases).

Drugs found to be weakly associated with DIIH included amiodarone, ciclosporin, combined oral contraceptives, danazol, fluoroquinolones (including ciprofloxacin, levofloxacin, nalidixic acid and ofloxacin), gonadotropin-releasing hormones, luteinising hormone stimulants, subcutaneous implantable progestogen-only contraceptives (Nexplanon and Norplant), stanozolol, sulfasalazine, sufentanil, ustekinumab and valproate semisodium (divalproic acid).

“We suggest using the term ‘drug-induced intracranial hypertension’ (DIIH) and propose a set of diagnostic criteria for DIIH… This may ultimately assist physicians in counselling patients about the risk of DIIH when prescribing medications and recognizing this uncommon yet sight-threatening condition”, said the authors. “If DIIH is suspected by the physician, a timely referral for co-evaluation and co-management by a neurologist and an ophthalmologist is recommended”, they commented.

Tan MG, Worley B, Kim WB, et al. Drug-induced intracranial hypertension: a systematic review and critical assessment of drug-induced causes. Am J Clin Dermatol. Epub 18 Nov 2019. http://doi.org/10.1007/s40257-019-00485-z. Accessed 11 Dec 2019.

16 Medication Error Safety Concerns Associated with Approved Drugs

Despite premarketing efforts to reduce the risk of medication errors (MEs) and a mandatory EU Risk Management Plan for all newly licensed medicinal products, over a quarter of centrally authorised products in the European Economic Area (EEA) are associated with ME safety concerns, according to findings of a study published in Drug Safety.

Data from the European Public Assessment Report registry were used to investigate ME safety concerns included in risk management plans of originator centrally authorised products which were authorised between 2010 and 2017 in the EEA. For each product, safety concerns, categories for the Summary of Safety Concerns, and how MEs were addressed, were assessed.

In total, 311 centrally authorised products were approved during the study period, and 84 (27%) of the products had a total of 95 ME safety concerns. The proportion of products with ME safety concerns ranged from 15.2% in 2011 to 36.4% in 2015. The most frequent types of ME were drug administration error (n = 17), product dosage form confusion (n = 10) and product preparation error (n = 9).

Additional risk minimisation measures (aRMMS) were required to address 27 ME safety concerns in 23 of the products, and included educational material for healthcare professionals (85.2%) and/or patients (51.9%). Studies evaluating the effectiveness of the additional measures were agreed upon for 78.3% of products with aRMMS for MEs.

“The high number of products with ME safety concerns and the high proportion of ME safety concerns with aRMMS suggest awareness regarding MEs at the level of the pharmaceutical industry and regulators. There is limited knowledge regarding the effectiveness of the measures available to prevent MEs. Therefore, studies are necessary to evaluate the suitability of the current risk minimisation framework for MEs”, said the authors.

Hoeve CE, Francisca RDC, Zomerdijk I, et al. Description of the risk management of medication errors for centrally authorised products in the European Union. Drug Saf. Epub 16 Oct 2019. https://doi.org/10.1007/s40264-019-00874-7. Accessed 11 Dec 2019.
17 Drug-Related Problems in COPD Exacerbation

In patients hospitalised for an exacerbation of chronic obstructive pulmonary disease (COPD), there is a high prevalence of drug-related problems, according to study results reported in Drug Safety.

The study was conducted in an academic teaching hospital in China. Drug-related problems and interventions were analysed based on the Pharmaceutical Care Network Europe (PCNE)-DRP V8.02 classification, where one problem (P) may have multiple causes (C) and lead to more than one intervention (I) but lead to only one outcome (O).

There were 640 drug-related problems in 393 patients, or an average of 1.6 per patient, which had 763 corresponding causes. At least one problem occurred in 223 patients (56.7%). The major type of problem identified was “treatment causes. At least one problem occurred in 223 patients or an average of 1.6 per patient, which had 763 corresponding causes. At least one problem occurred in 223 patients (56.7%). The major type of problem identified was “treatment safety P2” (54.2%), followed by “treatment effectiveness P1” (24.1%). The most frequently identified cause of the problem was “drug selection C1” (24.2%), followed by “dose selection C3” (21.5%) and “treatment duration C4” (21.7%). The three major cause subcategories were drug dose too high, duration of treatment too long, and patient administers/uses the drug in a wrong way. “This indicates that the pharmacist should provide necessary patient education on the correct use of drugs when providing medication review”, note the authors.

Most patients (96.9%) were receiving polypharmacy (≥ 5 medications), with an average of 11.2 medications per patient. The five most frequently used medication classes were antibiotics, antihypertensives, bronchodilators, corticosteroids, and expectorants. The drug class most frequently involved in drug-related problems was antibiotics (36.7%), followed by corticosteroids (19.8%) and proton pump inhibitors (10.2%).

In multivariate logistic regression analysis, there was a significant association with drug-related problems in patients with renal dysfunction, those taking ≥ 10 drugs, and those who are hospitalised for ≥ 8 days, and an association in patients with ≥ 3 comorbidities.

Pharmacists proposed 1557 interventions to solve the drug-related problems, an average of 2.4 per problem identified. These were mostly made at the “drug level I3” (45.5%), followed by at the “prescriber level I1” (32.6%) and at the “patient level I2” (16.2%). Overall, 91.0% of interventions were accepted, and 80.0% were fully implemented; 91.6% of problems were solved.

“Pharmacists can have an important role in addressing the problems and optimizing the safety and effectiveness of therapies for hospitalized COPD patients”, note the authors.

Li Q, Qu HJ, Ly D, et al. Drug-related problems among hospitalized patients with COPD in mainland China. Int J Clin Pharm. 2019;41(6):1507–15.

18 Impurity Testing of Ranitidine Products: US FDA Update

Ranitidine products containing n-nitrosodimethylamine (NDMA) levels above acceptable limits will be recalled in the US while investigations are ongoing into the contamination, says CDER Director Dr. Janet Woodcock.

A number of US-approved medicines containing ranitidine (commonly known as Zantac) have been tested over the past few months, and a summary of current investigation results was recently presented by Dr. Woodcock.

She noted that the CDER had “conducted tests that simulate what happens to ranitidine after it has been exposed to acid in the stomach with a normal diet and results of these tests indicate that NDMA is not formed through this process”. NDMA was also not formed when ranitidine was exposed to a simulated small intestine environment, but Dr. Woodcock noted that human trials still needed to be carried out to fully understand if ranitidine forms NDMA.

Although many NDMA levels observed in US FDA testing to date “are much lower than the levels some third-party scientists first claimed, some levels still exceed what the FDA considers acceptable for these medicines”, highlighted Dr. Woodcock. If the FDA or manufacturers find NDMA levels that are above acceptable limits (i.e. 96 ng/day, or 0.32 parts per million), then companies are being asked to voluntarily recall their ranitidine product(s).

In addition, manufacturers are being asked to voluntarily recall products containing nizatidine (commonly known as Axid, and chemically similar to ranitidine) if NDMA levels are found to be above the acceptable daily intake level. Manufacturers are also requested to continue conducting their own laboratory testing to assess NDMA levels in products containing ranitidine or nizatidine, and samples should also be sent to the FDA so that the agency could conduct its own tests.

To date, FDA testing of a ranitidine syrup commonly used in paediatric patients has revealed some samples with NDMA levels above the acceptable limits, which are now being recalled. Testing of a ranitidine injection is also ongoing.

Woodcock J. Statement on new testing results, including low levels of impurities in ranitidine drugs. 1 Nov 2019. https://www.fda.gov/news-events/press-announcements/statement-new-testing-results-including-low-levels-impurities-ranitidine-drugs. Accessed 11 Dec 2019.
19 ADHD Drugs not Associated with Serious CV Events in Children

Attention-deficit hyperactivity disorder (ADHD) medication does not appear to be associated with serious cardiovascular (SCV) events in children or adolescents with ADHD or autism spectrum disorder (ASD), according to findings of a F. Hoffmann-La Roche-funded study published in *CNS Drugs*.

Commercial claims data (2000–2016) and Medicaid claims data (2012–2016) from the US Truven Health MarketScan database were used to conduct nested case–control studies in paediatric patients 3–18 years of age with ADHD (n = 2,240,774) or ASD (326,221). Each case with the composite outcome of stroke, myocardial infarction (MI) or serious arrhythmias was matched with ten controls based on age, sex and insurance type. Conditional logistic regression analysis was used to evaluate the associations between SCV events and current ADHD medication use including CNS stimulants such as methylphenidate or non-stimulants such as atomoxetine.

The risk of SCV events was not significantly increased in patients with ADHD or ASD; in the ADHD cohort 33.9% of cases and 32.2% of controls were exposed to ADHD medication (OR 1.08; 95% CI 0.78, 1.49), while in the ASD cohort 12.5% of cases and 22.1% of controls were exposed to ADHD drugs (OR 0.49; 95% CI 0.20, 1.20). There was also no increased risk of SCV events after adjustment for covariates, or for individual SCV outcomes.

“In conclusion, in a large, contemporary insurance database, we found low rates of SCV events in children and adolescents with ADHD or ASD; in the ADHD cohort 33.9% of cases and 32.2% of controls were exposed to ADHD medication (OR 1.08; 95% CI 0.78, 1.49), while in the ASD cohort 12.5% of cases and 22.1% of controls were exposed to ADHD drugs (OR 0.49; 95% CI 0.20, 1.20). There was also no increased risk of SCV events after adjustment for covariates, or for individual SCV outcomes.”

Houghton R, de Vries F, Loss G. Psychostimulants/atomoxetine and serious cardiovascular events in children with ADHD or autism spectrum disorder. *CNS Drugs*. Epub 25 Nov 2019. http://doi.org/10.1007/s40263-019-00686-4. Accessed 11 Dec 2019.

20 ADRs in High-Risk Pregnancy

Magnesium sulphate is the drug most frequently associated with ADRs in women with high-risk pregnancy in Brazil, according to findings of a study published in the *European Journal of Clinical Pharmacy*.

ADRs were investigated in 607 women with high-risk pregnancies admitted to an obstetric intensive care unit (ICU) in Brazil between June 2016 and December 2017. Patients were excluded if they were admitted to the ICU for non-obstetric conditions, stayed in the ICU for less than 24 h, or were readmitted to the ICU.

The overall incidence of ADRs was 27.2%. No severe ADRs were reported but 29.7% of ADRs were of moderate severity.

The incidence of ADRs was highest in patients receiving magnesium sulphate (44.5%), and was much lower for all other drugs, including vancomycin (14.3%), meropenem (9.2%), cefalexin (5.3%), azithromycin (4.5%), methylprednisolone (2.6%), mineral oil (1.4%), insulin (1.1%), ferrous sulphate (0.5%) and captopril (0.3%).

ADRs reported in patients receiving magnesium sulphate included somnolence (68.6%), absent patellar reflex (21.6%) and hypotension (9.8%). All four cases of methylprednisolone-related ADRs were somnolence. Moderate hypoglycaemia was reported in one patient receiving insulin, and mild diarrhoea was reported in patients receiving azithromycin, cefalexin, meropenem, ferrous sulphate and vancomycin (one case each).

Multivariate analysis found that higher BP (adjusted odds ratio [aOR] 1.02), higher haemoglobin level (aOR 1.21) and lower body temperature (aOR 0.71) significantly increased the risk of ADRs.

Considering its therapeutic importance in preeclampsia/eclampsia and for foetal neuroprotection, the benefits of magnesium sulphate to the mother and foetus outweigh its risks, even though its use is associated with significant ADR, said the investigators.

Xavier da Costa T, de Almeida Pimenta Cunha MD, do Vale Bezerra PK, et al. Incidence of adverse drug reactions in high-risk pregnancy: a prospective cohort study in obstetric intensive care. *Eur J Clin Pharmacol*. Epub 25 Nov 2019. https://doi.org/10.1007/s00228-019-02789-9. Accessed 11 Dec 2019.

21 Interstitial Lung Disease Risk with Prostate Cancer Meds

The risk of interstitial lung disease will be added to the package inserts for two prostate cancer medicines—apalutamide and enzalutamide, according to Japan’s Pharmaceuticals and Medical Devices Agency (PMDA).

Apalutamide (Erleada Tablets) is indicated for treatment of castration-resistant prostate cancer without remote metastasis. Since the launch of this product in Japan in May 2019, there have been a total of four cases involving interstitial lung disease (including two cases for which a causal relationship to the drug could not be ruled out). In addition, there has been one patient death reported to date, but again, a causal relationship between the drug and death subsequent
to the patient’s interstitial lung disease could not be ruled out [1].

Enzalutamide (Xtandi Capsules, Xtandi Tablets) is indicated for the treatment of castration-resistant prostate cancer. Over the past 3 fiscal years in Japan, a total of 19 cases involving interstitial lung disease have been reported to date (including five cases for which a causal relationship to the drug could not be ruled out). Furthermore, three patient deaths have been reported, but a causal relationship between the drug and deaths could not be established in any of these cases [2].

Based on its investigation of currently available evidence and consultation with expert advisors, the MHLW/PMDA concluded that the following package insert revisions are necessary for both apalutamide and enzalutamide:

- “Patients with interstitial lung disease or a history of the disease” should be added to the “Careful Administration” section.
- A cautionary statement for interstitial lung disease should be added to the “Important Precautions” section.
- “Interstitial lung disease” should be added to the “Clinically Significant Adverse Reactions” section.

1. Pharmaceuticals and Medical Devices Agency of Japan. Summary of investigation results - apalutamide. 15 Nov 2019. http://www.pmda.go.jp/files/0002322288.pdf. Accessed 11 Dec 2019.
2. Pharmaceuticals and Medical Devices Agency of Japan. Summary of investigation results—enzalutamide. 15 Nov 2019. http://www.pmda.go.jp/files/0002322289.pdf. Accessed 11 Dec 2019.

### 22 Statins not Associated with Memory or Cognitive Decline

Treatment with statins does not appear to be associated with memory or cognitive disorders in elderly patients, according to findings of the Sydney Memory and Aging Study published in the *Journal of the American College of Cardiology (JACC)* [1].

This prospective study investigated the effects of statins (atorvastatin, pravastatin or simvastatin) on memory and global cognition over a 6-year period in 1037 community-dwelling patients in Australia who were 70–90 years of age, and the effects of statins on brain volume over a 2-year period in a subgroup of 526 patients. Five memory tests and 12 cognitive tests were used. Brain volume was assessed using magnetic resonance imaging.

Rates of memory decline and global cognitive decline did not differ significantly between statin users and patients who never used statins.

- Overall, initiation of statins was associated with a reduced rate of memory decline. Statin use was associated with attenuated decline in memory test performance in patients with heart disorders and those with the apolipoprotein Eε4 (ApoEε4) genotype.
- Changes in brain volume did not differ significantly between statin users and non-users.
- “Statin use in the elderly population was not associated with any acceleration in decline in memory, global cognition, or brain volumes… Protective associations were found for some aspects of memory testing in those with dementia risk factors such as heart disease and ApoEε4 gene carriage”, concluded the investigators.
- “Contrary to popular concern, statin use was not associated with cognitive decline in this observational study”, said Drs. Constantino Iadecola and Neal Parikh from Weill Cornell Medicine, New York, USA, in an accompanying editorial published in the *JACC* [2]. “These data support the view that worries about cognitive impairment should not limit statin use and raise the possibility that statins may favorably alter cognitive trajectories in a group of elderly subjects at high risk of Alzheimer disease”, they commented.

1. Samaras K, Makkar SR, Crawford JD, et al. Effects of statins on memory, cognition, and brain volume in the elderly. J Am Coll Cardiol. 2019;74(21):2554–68.
2. Iadecola C, Parikh NS. Statins and cognitive impairment: not a culprit, protective in some? J Am Coll Cardiol. 2019;74(21):2569–71.

### 23 Surveillance of 9v HPV Vaccine Safety

The low uptake of human papillomavirus (HPV) vaccines in the USA may be due to concerns about vaccine safety. Two studies reported in *Pediatrics* investigated the safety of the 9-valent HPV vaccine [9vHPV vaccine; Gardasil 9].

#### 23.1 Reports to VAERS

The first study investigated 7244 postlicensure surveillance reports to the US FDA’s Vaccine Adverse Event Reporting System (VAERS) from December 2014 until December 2017 [1]. Most reports were submitted by the vaccine manufacturer (64.2%), with 26.8% of reports submitted by healthcare providers. Disproportional reporting was evaluated using empirical Bayesian data mining.

Most reports (97.4%) were not classified as serious, and 9vHPV vaccine was given alone in 74.7% of reports. Two
deaths were reported, but “no information in autopsy reports or death certificates suggested a causal relationship with vaccination”, note the authors. The most commonly reported events were dizziness (7.5%), syncope (6.9%), headache (5.0%), and injection site pain (4.5%) or erythema (4.4%). As about 28 million doses of 9vHPV vaccine were distributed during the study period, the crude adverse event reporting rate was 259 per million doses overall and 7 per million doses for serious events. The rate for syncope was 26 per million doses, which did exceed the threshold for disproportional reporting, but is a known adverse event for injectable vaccines. Rates for all other events were < 1 per million doses.

Analysis of prespecified conditions revealed 9 reports of anaphylaxis, 8 reports of Guillain-Barré syndrome, 17 reports of postural orthostatic tachycardia syndrome, 3 reports of primary ovarian insufficiency, 1 report of complex regional pain syndrome, and 2 reports of acute disseminated encephalomyelitis. However the authors note that “most reported events did not meet diagnostic criteria or did not contain sufficient information to make a determination on the diagnosis”.

The authors conclude that “no new or unexpected safety concerns or reporting patterns of 9vHPV with clinically important AEs were detected”.

### 23.2 Reports to VSD

The second study investigated reports to the Vaccine Safety Datalink (VSD) between October 2015 and October 2017 in patients 9–26 years of age, when 838,991 vaccine doses were administered [2]. Rapid Cycle Analysis (RSA) methodology was used to compare adverse events in recently vaccinated and unvaccinated groups, with near real-time data. Relative risks were investigated using maximised sequential probability ratio test (MaxSPRT), conditional MaxSPRT (cMaxSPRT) and exact sequential analysis (ESA) analyses.

Unexpected statistical signals were detected for the following events: pancreatitis in men 18–26 years of age after any dose; appendicitis after dose 3 in boys 9–17 years of age; allergic reactions after dose 2 in women 18–26 years of age; and allergic reactions in girls 9–17 years of age after any dose. Further investigation did not confirm signal generation, with results classified as false-positives. Signals were also detected for syncope, injection site reactions, and nonspecific reactions, but no further investigations were conducted because they were “expected based on clinical trials of 9vHPV”, note the authors, “and because the diagnoses were unlikely to indicate a serious adverse event’. They add that “with this large observational study, we contribute reassuring postlicensure data that will help bolster the safety profile of 9vHPV”.

### 23.3 Vaccine Development

In an accompanying commentary reported in *Pediatrics*, Cody Meissner (Tufts University, USA) notes that development of antiviral vaccines began when Peyton Rous postulated in the early 1900s that sarcoma transmission between hens may be virus-related, followed by identification in 1964 of the first human DNA tumour virus, the Epstein-Barr virus. Papillomavirus DNA was isolated in 1983, with > 120 types of HPV subsequently classified; the first HPV vaccine was licensed in the USA in 2006 [3]. He notes that “the availability of the 9vHPV is one end of a remarkable journey of discovery and progress to develop a safe and effective vaccine to prevent suffering and death from a common cancer”. In addition, “≈ 33,600 cancers are caused by HPV each year in the United States”, and “approximately 90% of these cancers could be prevented by routine administration of the 9-valent human papillomavirus vaccine… early in life”. He concludes that “deferral of HPV vaccination because of questions regarding safety can no longer be defended as a reasonable option”.

1. Shimabukuro TT, Su JR, Marquez PL, et al. Safety of the 9-valent human papillomavirus vaccine. Pediatrics. 2019;144(6):e20191791.
2. Donahue JG, Kieke BA, Lewis EM, et al. Near real-time surveillance to assess the safety of the 9-valent human papillomavirus vaccine. Pediatrics. 2019;44(6):e20191808.
3. Meissner HC. From Peyton Rous to the HPV vaccine: a journey of discovery and progress. Pediatrics. 2019;44(6):e20192345.

### 24 Many Antibacterials Associated with Acute Kidney Injury

Many antibacterials appear to be associated with acute kidney injury (AKI), according to findings of a study published in *Drug Safety* that was based on FAERS reports. FAERS data from 2,042,801 reports over a 3-year period (2015–2017) were used to determine reporting odds ratios (RORs) for associations between antibacterials (intramuscular, intravenous, subcutaneous or parenteral) and AKIs. There were 20,138 reports of AKI to FAERS during the study period.

RORs for AKI were significant for colistin (ROR 33.10; 95% CI 21.24, 51.56), aminoglycosides (ROR 17.41; 95% CI 14.49, 20.90), vancomycin (ROR 15.28; 95% CI 13.82, 16.90), cotrimoxazole (trimethoprim/sulfamethoxazole; ROR 13.72; 95% CI 11.94, 15.76), penicillin combination therapy (ROR 7.95; 95% CI 7.09, 8.91), clindamycin (ROR 6.46; 95% CI 5.18, 8.04), cefalosporins
(ROR 6.07; 95% CI 5.23, 7.05), daptomycin (ROR 6.07; 95% CI 4.61, 7.99), macrolides (ROR 3.60; 95% CI 3.04, 4.26), linezolid (ROR 3.48; 95% CI 2.54, 4.77), carbapenems (ROR 3.31; 95% CI 2.58, 4.25), metronidazole (ROR 2.55; 95% CI 1.94, 3.36), tetracyclines (ROR 1.73; 95% CI 1.26, 2.36), and fluoroquinolones (ROR 1.71; 95% CI 1.49, 1.97).

“This study found 14 classes of antibiotics having significant reporting associations with AKI. Among the antibiotics evaluated in this study, colistin had the highest AKI ROR and moxifloxacin had the lowest”, concluded the authors. “Of the macrolides and fluoroquinolones, only azithromycin and moxifloxacin did not have significant reporting associations with AKI”, they noted.

Patek TM, Teng C, Kennedy KE, et al. Comparing acute kidney injury reports among antibiotics: a pharmacovigilance study of the FDA Adverse Event Reporting System (FAERS). Drug Saf. Epub 18 Oct 2019. https://doi.org/10.1007/s40264-019-00873-8. Accessed 11 Dec 2019.

25  Angiotensin Receptor Antagonists Increase Risk of Suicide

Angiotensin receptor blockers (ARBs) appear to increase the risk of suicide in elderly patients compared with ACE inhibitors (ACEIs), according to findings of a Canadian case-control study published in JAMA Network Open [1].

Data from administrative claims databases in Ontario (1995–2015) were used to investigate death by suicide during treatment with ARBs or ACEIs in patients 66 years of age and over. Conditional logistic regression analysis was used to assess the association between suicide and exposure to ARBs versus ACEIs in 964 patients who died by suicide within 100 days of receiving an ACEI or ARB (cases) compared with 3856 ACEI- or ARB-treated patients matched by age, sex and comorbid hypertension and diabetes mellitus who did not die by suicide (controls).

Of patients exposed to ARBs (most frequently candesartan, telmisartan or valsartan), 26.0% were cases and 74.0% were controls, while of patients exposed to ACEIs (most frequently enalapril or ramipril), 18.4% were cases and 81.6% were controls.

Treatment with ARBs significantly increased the risk of death by suicide compared with treatment with ACEIs (aOR 1.63; 95% CI 1.33, 2.00). Sensitivity analysis showed similar findings after exclusion of patients with a history of self-harm (aOR 1.60; 95% CI 1.29, 1.98).

“Our findings suggest a possible increased risk of suicide associated with the use of ARBs compared with ACEIs among adults aged 66 years and older. Given their high prevalence of use, the severity of the outcome, and the similar efficacy of these drug classes in treating the same conditions, clinicians may opt for preferential use of ACEIs over ARBs where possible”, concluded the authors.

“The report by Mamdani et al. that ARBs are associated with increases in the risk of suicide in a study using real-world data requires conceptual replication. The strength of the methods, the importance of preventing suicide, and the number of people exposed to ARBs all support the need to encourage additional studies and to translate the combined findings into guidance about prescribing”, said Dr. Ira Katz from the Office of Mental Health and Suicide Prevention, Department of Veterans Affairs, Philadelphia, Pennsylvania, USA, in an accompanying invited commentary published in JAMA Network Open [2].

1. Mamdani M, Gomes T, Greaves S, et al. Association between angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and suicide. JAMA Netw Open. Epub 16 Oct 2019. http://dx.doi.org/10.1001/jamanetworkopen.2019.13304. Accessed 11 Dec 2019.

2. Katz IR. Concerns raised by a study of suicide as an adverse drug effect—replicating findings from real-world data. JAMA Netw Open. Epub 16 Oct 2019. http://dx.doi.org/10.1001/jamanetworkopen.2019.13284. Accessed 11 Dec 2019.

26 New Safety Signals for Asthma Drugs in Children

Analysis of spontaneous ADR reports to the European Medicine Agency’s EudraVigilance database has identified new safety signals for asthma drugs in paediatric patients, say authors of a study published in Drug Safety.

A proportional reporting ratio (PRR) was calculated for each asthma drug-event combination (DEC) reported to EudraVigilance between 2011 and 2017. Signals in paediatric patients up to 17 years of age were compared with those in the total patient population.

Among the 372,345 reports in pediatric patients, there were 21,264 antiasthmatic-related DECs associated with single drug or fixed-dose combinations. There were 3697 unique DEC- or ARB-treated patients matched by age, sex and comorbid hypertension and diabetes mellitus who did not die by suicide (controls).

Treatment with ARBs significantly increased the risk of death by suicide compared with treatment with ACEIs (aOR 1.63; 95% CI 1.33, 2.00). Sensitivity analysis showed similar findings after exclusion of patients with a history of self-harm (aOR 1.60; 95% CI 1.29, 1.98).

“Our findings suggest a possible increased risk of suicide associated with the use of ARBs compared with ACEIs among adults aged 66 years and older. Given their high prevalence of use, the severity of the outcome, and the similar efficacy of these drug classes in treating the same conditions, clinicians may opt for preferential use of ACEIs over ARBs where possible”, concluded the authors.

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1. Mamdani M, Gomes T, Greaves S, et al. Association between angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and suicide. JAMA Netw Open. Epub 16 Oct 2019. http://dx.doi.org/10.1001/jamanetworkopen.2019.13304. Accessed 11 Dec 2019.

2. Katz IR. Concerns raised by a study of suicide as an adverse drug effect—replicating findings from real-world data. JAMA Netw Open. Epub 16 Oct 2019. http://dx.doi.org/10.1001/jamanetworkopen.2019.13284. Accessed 11 Dec 2019.
13 reports) and fluticasone-associated adrenal cortical hypofunction (PRR 59.5; 95% CI 39.1, 90.4; 22 reports). All ten signals with the highest PRRs were already known. There were 30 signals classified as new. New signals unmasked by calculating the PRR by therapeutic area included herpes virus infections and bacterial infections associated with omalizumab, and herpes virus infections associated with budesonide. Other new signals included hypertrichoses with budesonide and encephalopathy with theophylline. Overall, 16% of the signals in paediatric patients did not appear in the total patient population.

“Although 92% of the statistical signals were already known, we observed 30 new signals, especially for omalizumab. Calculation of the PRR by therapeutic area, age and sex revealed additional new signals, pointing to masking due to confounding by indication or effect modification… Safety signals of asthma drugs were mainly related to psychiatric disorders, especially in combination with the use of montelukast”, said the authors.

Baan EJ, de Smet VA, Hoeve CE, et al. Exploratory study of signals for asthma drugs in children, using the EudraVigilance database of spontaneous reports. Drug Saf. Epub 15 Oct 2019. https://doi.org/10.1007/s40264-019-00870-x. Accessed 11 Dec 2019.