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UPDATE

Forum

1 Web Service in Denmark for ADR Reporting

A web service launched in 2014 in Denmark to facilitate reporting of adverse drug reactions (ADRs) by doctors, dentists and midwives is not yet fully utilised and there appears to be limited awareness of the service, according to the Danish Medicines Agency.

To date, only three out of eight medical practice systems in Denmark have implemented the new web service. The Danish Medicines Agency is working to spread knowledge about the service, which enables the possibility of embedding ADR reporting into local practice systems directly, providing healthcare professionals with an easier and quicker way to report ADRs.

As well as being able to send reports directly from electronic patient records at a hospital or a medical practice, the web service eliminates the need to enter basic information manually by auto-filling parts of the report from the patient record. Auto-filled data can include information on the patient who experienced the ADR, details on current medication the patient is taking, and healthcare professions' notes and details, all of which are mandatory information in an ADR report.

Danish Medicines Agency. Renewed focus on IT tool to facilitate the reporting of adverse reactions. DKMA Update 2018;2(2):8.

2 Inconsistent Labelling for Drug Interactions in US, EU

There are labelling inconsistencies in the drug-drug ADR information provided by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA), according to the Uppsala Monitoring Centre (UMC).

UMC representatives Sofia Zappacosta, Sarah Watson and Marian Attalia discussed four drug-drug ADR combinations that were highlighted in VigiBase searches during signal detection screening.

Metformin, in combination with either ciprofloxacin or levofloxacin, are suspected of causing hypoglycaemia. In the US, the warning is present on the labelling for the antibacterials, but not so for metformin. In the UK, the metformin labelling does not mention the potential interaction with ciprofloxacin or levofloxacin, but it is mentioned in the labelling for levofloxacin itself.

Secondly, sertraline given in combination with quetiapine has been linked to the development of serotonin syndrome (SS) and/or neuroleptic malignant syndrome (NMS). SS is a potentially life-threatening condition, for which signs and symptoms can include mental status changes, seizures, and neuromuscular symptoms. NMS is characterised by similar symptoms to SS (e.g. altered mental status, muscular rigidity and tremor).

As of 10 November 2017, there were almost 30 reports in which sertraline and quetiapine were co-reported as suspected/interacting drugs in relation to SS, and 15 reports for NMS. The Summary of Product Characteristics (SmPC) for sertraline in the UK mentions the risk of SS or NMS when taken concomitantly with antipsychotics (e.g. quetiapine). Quetiapine itself has also been associated with cases of NMS. However, there is no mention of an increased risk of SS, when used in combination with sertraline, in the labelling for quetiapine.

Next, co-administration of tacrolimus and mycophenolic acid has been associated with 24 reports of the adverse event referred to as "drug level increased". In the UK, the SmPC for mycophenolic acid mentions that the drug levels may increase when concurrently administered with tacrolimus. "However, the UK SmPC for tacrolimus does not mention this interaction", noted the UMC representatives.

Finally, aspirin (acetylsalicylic acid) and dipyridamole (i.e. platelet aggregation inhibitor) have been associated with reports of melaena. Melaena refers to dark black, tarry faeces that are associated with upper gastrointestinal bleeding.

In VigiBase, there are 30 reports of melaena associated with these two drugs, but this increases to 85 reports when the term "gastrointestinal haemorrhage" is added. A

fixed-combination pill is available in the US and EU, but the labels give contradictory information regarding this safety risk. There is also inconsistent information regarding the increased risk of gastrointestinal bleeding in the labelling for the individual drugs.

Zappacosta S, Watson S, Attalia M. Inconsistent labelling for drug interactions. WHO Pharmaceuticals Newsletter 2018;16–7(4):16.

3 PHARMAC Changing Funded Access to Drugs for Rare Diseases

New Zealand's Pharmaceutical Management Agency (PHARMAC) is working towards improving funded access to drugs for the treatment of rare diseases, and has now appointed a clinical subcommittee with expertise in this field to provide advice to its Pharmacology and Therapeutics Advisory Committee (PTAC).

PHARMAC has also published updated policy settings for assessing drugs for rare disorders, and opened a commercial process seeking funding applications from manufacturers of medicines for rare disorders.

"The updated policy settings help define which medicines we will consider in this process, and provide certainty to stakeholders of the sort of medicines we are looking for," said PHARMAC's Chief Executive, Sarah Fitt.

PHARMAC is also widening access to funded enzyme replacement therapy for Gaucher's disease, and is phasing in taliglucerase for treatment of this rare disorder from August 2018, to replace imiglucerase.

Pharmaceutical Management Agency. PHARMAC work in funding medicines for rare disorders progressing. 2018 Jul 16 [online]. Available from URL: https://www.pharmac.govt.nz/news/media-2018-07-16-rare-disorders. Accessed 19 Sep 2018.

4 Health Canada's Mandatory Hospital-Based Reporting

Health Canada has invited email feedback from all interested Canadians on their draft guideline document regarding proposed amendments to the Food and Drug Regulations and Medical Device Regulations. Hospitals would be required to report serious ADRs, or medical device incidents, to the agency.

The guidance document provides information which may be useful to achieve reporting compliance. Input is requested regarding the clarity and detail of the descriptions and instructions, whether the guidance interpretations are workable in the hospital setting, and whether further information is required to understand both the regulations and what is required of the reporters. The consultation period ended on 29 August 2018.

Health Canada. Consultation on draft guidance document for Hospital-Based Mandatory Reporting Regulations (Vanessa's Law). 2018 Jul 13 [online]. Available from URL: https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/medeffect-canada/consultation-draft-guidance-hospital-mandatory-reporting-regulations.html. Accessed 19 Sep 2018.

5 PMDA Labelling Changes Regarding Neuropsychiatric Symptoms

A number of products available in Japan will have their package inserts revised in terms of the language used to describe neuropsychiatric symptoms, says Japan's Pharmaceuticals and Medical Devices Agency (PMDA).

Specifically, reports of abnormal behaviour have been made following use of the following products: amantadine, oseltamivir, zanamivir, laninamivir, baloxavir marboxil, favipiravir and peramivir [1–6].

As a result, revisions will be made to the package inserts for the above-mentioned products, including changes to the respective 'Important Precautions' sections, as well as the addition of the following statement to the 'Clinically Significant Adverse Reactions' subsection:

- "Abnormal behaviour (such as sudden movement, or wandering) that could result in falls etc. may occur in patients infected with influenza, although the existence of a causal relationship between these symptoms and this drug is currently unclear".

Examples of such neuropsychiatric symptoms (including disturbed consciousness, coma, delirium, hallucinations, delusions, and confusion) will also be mentioned where appropriate in the respective package inserts.

However, for amantadine specifically, other conditions will also be added to the 'Clinically Significant Adverse Reactions' subsection, including convulsions and myoclonus.

1. Pharmaceuticals and Medical Devices Agency of Japan. Revision of precautions—amantadine hydrochloride. 2018 Aug 21 [online]. Available from URL: http://www.pmda.go.jp/files/000225502.pdf. Accessed 19 Sep 2018.
2. Pharmaceuticals and Medical Devices Agency of Japan. Revision of precautions—oseltamivir phosphate. 2018 Aug 21 [online]. Available from URL: http://www.pmda.go.jp/files/000225504.pdf. Accessed 19 Sep 2018.
3. Pharmaceuticals and Medical Devices Agency of Japan. Revision of precautions—zanamivir hydrate, laninamivir octanoate hydrate. 2018 Aug 21 [online]. Available from URL: http://www.pmda.go.jp/files/000225506.pdf.

4. Pharmaceuticals and Medical Devices Agency of Japan. Revision of precautions—baloxavir marboxil. 2018 Aug 21 [online]. Available from URL: http://www.pmda.go.jp/files/000225508.pdf. Accessed 19 Sep 2018.
5. Pharmaceuticals and Medical Devices Agency of Japan. Revision of precautions—favipiravir. 2018 Aug 21 [online]. Available from URL: http://www.pmda.go.jp/files/000225509.pdf. Accessed 19 Sep 2018.
6. Pharmaceuticals and Medical Devices Agency of Japan. Revisions of precautions—peramivir hydrate. 2018 Aug 21 [online]. Available from URL: http://www.pmda.go.jp/files/000225511.pdf. Accessed 19 Sep 2018.

6 EMA Scales Back Clinical Trial Transparency Policies

The EMA has scaled back transparency policies for landmark clinical trials due to the high workload and staff losses in preparation for Brexit, reported Peter Doshi in the *BMJ*.

A freedom-of-information policy granting public access to documents and clinical trial data in EMA's archives (policy 0043) is now restricted to EU citizens only, while processing of new data packages under the EMA's clinical data publication policy (policy 0070) has been suspended since 1 August 2018.

These measures have been criticised by transparency advocates. "Deaths and other serious harms are much under-reported in published trials, and we therefore need unhindered and immediate access to clinical study reports and other relevant documentation that the EMA holds," said Peter Gøtzsche, director of the Nordic Cochrane Centre. "The Brexit induced scale back and suspension of activities by the EMA is a major threat to open and transparent access to important clinical data. Without this data, it may not be fully possible to independently appraise, synthesise, and implement important information related to the use of medicines in the UK," said Dr Kamal Mahtani, deputy director of the Centre for Evidence Based Medicine at the University of Oxford.

EMA spokesperson Henry Fitt said it is unclear how requests from the UK will be dealt with after Brexit. The EMA "will do its utmost to resume the proactive publication of clinical data" after relocation to Amsterdam in March 2019 is complete, according to a report on its website. However, the policy granting public access that is no longer available outside the EU "is not a temporary measure and we are not currently planning on revisiting this decision," said the EMA.

Doshi P. EMA scales back transparency initiatives because of workload BMJ 2018;362:k3513.

7 Blockchain Technology Offers Potential in Healthcare

Blockchain technology, a secure decentralised database which stores a registry of assets and transactions across a peer-to-peer computer network, offers potential in healthcare organisations and medical practices, say authors of an article published in *Applied Health Economics and Health Policy*.

Blockchain technology is currently primarily used for Bitcoin digital currency, but it is expected to have future uses in medicine, science, education, intellectual property, and supply chain management. Possible applications include health records, health insurance, biomedical research, drug supply and procurement processes, and medical education. Projects currently under development include implementation of blockchain in electronic medical records, drug supply chain management, public health, health insurance, and education.

To date, blockchain technology is immature and lacks expert knowledge, making it hard to have a clear vision of its future potential, and there are issues with regard to scalability, security of smart contracts, and user adoption.

"Nevertheless, with capital investments into blockchain technology projected to reach US$400 million in 2019, health professionals and decision makers should be aware of the transformative potential that blockchain technology offers for healthcare organizations and medical practice," said the authors.

Radanovic I, Likic R. Opportunities for use of blockchain technology in medicine. Appl Health Econ Health Pol 2018;16(5):583–90.

8 HTAs Need Patient Input to Create Patient-Centred Healthcare Policy

Health technology assessments (HTAs) should consider patient-based evidence including preferences and experiences of patients, in order to support the development of patient-centered healthcare policy, say authors of an article published in *The Patient—Patient-Centered Outcomes Research*.

Although HTAs in the 1990s included rigorous research to produce patient-based evidence, HTAs in the 2000s became more closely linked to reimbursement decisions, and focused on clinical effectiveness and cost effectiveness, the authors said.

Patient involvement should be tailored to the needs of each HTA. As the timeframe for HTAs has reduced, research to produce patient-based evidence has been replaced by input from patient groups, placing a burden on individual patients and organisations that needs to be critically reviewed if the

goal of informing evidence-based patient-centred policy is to be achieved. It is important to clarify when patient involvement is likely to add value, and to support patients to provide their knowledge in the optimal way to influence HTA decision-making. However, HTA agencies do not pay patient groups for their submissions and few agencies offer payment for attending committee meetings, raising questions about how patient involvement in HTA should be funded, said the authors.

To reduce the burden on patient groups, researchers should be encouraged to produce patient-based evidence early in the development of new technologies. Research programmes should be carefully planned, with appropriate methodological rigour for each study, and all research should be published, according to the authors. The development of quality standards for research to produce patient-based evidence may be needed to achieve this. Patient involvement should be focused, systematic and transparent, and evolve according to the experiences of all stakeholders.

"Regardless of how HTA evolves, we need to ensure that its processes are robust, inclusive and evidence-based, genuinely incorporating patients' perspectives and experiences. HTA can then help to create patient-centred healthcare policy that ensures the fair and transparent allocation of resources informed by the needs, preferences and experiences of patients," concluded the authors.

Facey KM, Bedlington N, Berglas S, et al. Putting patients at the centre of healthcare: progress and challenges for health technology assessments. Patient. Epub 27 Jul 2018. https://doi.org/10.1007/s40271-018-0325-5. Accessed 19 Sep 2018.

9 Prescription Drugs Commonly Used By US Children, Adolescents

Many children and adolescents in the US use prescription drugs, and nearly 1 in 12 concurrent users are at risk of major drug-drug interactions (DDIs), say US researchers.

Utilising nationally representative data from NHANES, a nationally representative survey sampled from the US civilian, non-institutionalised population conducted by the National Center for Health Statistics, a total of > 23 000 paediatric patients aged 0–19 years who responded to prescription medication questionnaires were included in this analysis. Concurrent use of prescription medicines was defined as use of ≥ 2 such medications.

During 2013 and 2014, almost 20% of children and adolescents used ≥ 1 prescription medication, and approximately 7% used acute medications (i.e. used for ≤ 30 days).

Concurrent use of prescription medications was 7.5% overall, with the highest use occurring among boys aged 6–12 years (12%) and both boys and girls aged 13–19 years (10% for both).

The researchers noted that respiratory agents (e.g. bronchodilators, leukotriene modifiers) and psychotropic medications (including antidepressants, atypical antipsychotics and CNS stimulants) were among the most prevalent concurrently used medications.

Utilising pooled data from 2009 to 2014, the researchers found that 8.2% of concurrent users of prescription medications were at risk of a potentially major DDI. In addition, the vast majority of interacting drug regimens included antidepressants, and the use of combinations with potential major DDIs was significantly higher among adolescent girls versus boys (18.1% vs 6.6%).

The researchers noted that they "also found that prescription medications associated with an increased risk of suicidality are commonly used in children and adolescents and are often used together".

Efforts to prevent ADRs in children and adolescents should consider the role of interacting drug combinations, particularly in adolescent girls, concluded the researchers.

Qato DM, Alexander GC, Guadamuz JS, et al. Prescription medication use among children and adolescents in the United States. Pediatrics 2018;142(3):e20181042.

10 New Recommendations to Avoid Medication, Testing Errors

A new report from The Partnership for Health IT Patient Safety now identifies ways that technology can avoid medication and testing errors, says the Institute for Safe Medication Practices (ISMP).

The private-sector partnership (of which the ISMP is a participant) provides a trusted platform for multiple stakeholders to collect and analyse safety events and hazards, identify and share promising solutions and safe practices, and inform policymakers and the broader healthcare community about priorities to make health IT safer.

The report, called "Health IT Safe Practices for Closing the Loop", is the fourth in a series of toolkits that is available for use by healthcare systems worldwide.

A workgroup was convened by the Partnership "to address safety issues related to tracking diagnostic test results and medication changes", stated the ISMP. "This issue, often referred to as "closing the loop", has long been a challenge in all practice settings", added the Institute.

Specifically, the report includes detailed strategies on how to "mitigate missed, delayed, and incorrect diagnoses

on diagnostic testing results and medication changes", explained the ISMP.

The detailed strategies were based on the following three key safe practice recommendations:

- To develop and apply IT solutions to communicate the right information to the right people, at the right time, and in the right format.
- To implement health IT solutions to track key areas.
- To use health IT to link and acknowledge the review of information and the documentation of the action(s) taken.

Institute for Safe Medication Practices. Partnership for Health IT Patient Safety releases new recommendations to avoid testing and medication mix-ups. 2018 Aug 9 [online]. Available from URL: https://www.ismp.org/news/partnership-health-it-patient-safety-releases-new-recommendations-avoid-testing-and-medication. Accessed 19 Sep 2018.

11 TGA Releases 2017 Statistics for PV of Medicines, Vaccines

The 2017 report on the postmarketing pharmacovigilance (PV) activities for medicines and vaccines in Australia is now available, says the Therapeutic Goods Administration (TGA).

Every year, the agency's Pharmacovigilance and Special Access Branch (PSAB) prepares this report for incorporation in the Department of Health's publication (Australian Statistics on Medicines) of suspected adverse events (AEs) reported following the use of medicines and vaccines available in Australia (including prescription medicines, over-the-counter products, and complementary medicines).

During 2017, approximately 18 600 AE reports were received by the TGA, with the majority of these being submitted by sponsors (~54%), followed by State and Territory Health Departments (~18%) and hospitals and/or hospital pharmacists (~10%).

Compared with previous years, the largest increases in the number of AE reports were from sponsors (up from 9080 in 2016, to 9998 in 2017) and State and Territory Health Departments (up from 2824 in 2016, to 3441 in 2017). The TGA noted that the increase in reports from the latter group "may relate, in part, to the continuation of enhanced surveillance for two additions to the National Immunisation Program in 2016—the 18-month diphtheria, tetanus and acellular pertussis-containing vaccine and Zostavax".

Also, the Advisory Committee on Medicines (ACM) was established on 1 January 2017, which provides independent medical and scientific advice to the Australian Minister of Health and the TGA, on issues regarding the safety, efficacy and quality of medicines supplied across the country.

Five issues of "Medicines Safety Update" were published on the TGA's website during 2017.

Therapeutic Goods Administration. Medicines and vaccines post-market vigilance—statistics for 2017. 2018 Aug 22 [online]. Available from URL: https://www.tga.gov.au/medicines-and-vaccines-post-market-vigilance-statistics-2017. Accessed 19 Sep 2018.

12 Using Claims Data to Predict Medication-Related Risks

Use of models using claims data to predict medication-related risks in elderly patients "discriminated well between patients with and without all-cause hospitalizations, potentially drug-induced hospitalizations, and mortality", according to study results reported in *Value in Health*.

The study used nationwide data involving patients from the German Statutory Health Insurance Fund (AOK) in 2010–2012. Random sampling of patients ≥65 years of age allocated 22 500 patients to the model's training set and 7500 patients to the validation set. The medication-based model predicting the risk for hospital admission apparent in routine claims data (MEDI-RADAR) tool involved individual STOPP/START criteria (screening tool of older persons' potentially inappropriate prescriptions/screening tool to alert doctors to the right treatment), concurrent medical conditions and time-varying drug exposure windows.

The MEDI-RADAR model's ability to discriminate between high- and low-risk patients regarding actually observed events was generally good, and comparable between all-cause hospitalisations (c-index [CI] 0.63; 95% CI 0.62, 0.64), potentially drug-induced hospitalisations (CI 0.67; 0.65, 0.68) and mortality (CI 0.78; 0.76, 0.80). The results were "internally consistent and robust", note the authors.

"Our study showed that a large number of the clinically defined explicit prescribing criteria from the STOPP/START list can be adapted to reliably predict adverse outcomes in claims data", note the authors, who add that "the good predictive performance supports the notion that routine monitoring of medication safety in individual patients is possible under almost real-time conditions". They conclude that "to assess its clinical utility, implementation of these criteria within an interventional program to optimize prescribing is desired to further evaluate the effectiveness of this approach".

Meid AD, Groll A, Heider D, et al. Prediction of drug-related risks using clinical context information in longitudinal claims data. Value Health. Epub 30 Jun 2018. https://doi.org/10.1016/j.jval.2018.05.007. Accessed 19 Sep 2018.

13 Methods, Findings of Cochrane Review on HPV Vaccines Criticised

A Cochrane review assessing the effect of human papillomavirus (HPV) vaccines on precursors to cervical cancer "was incomplete and ignored important evidence of bias", says Dr Lars Jørgensen from the Nordic Cochrane Centre and his colleagues.

They analysed results of this Cochrane review of HPV vaccines involving trial searches through to June 2017, and included 26 randomised trials with almost 73 500 women. Dr Jørgensen and his colleagues also published an index of the study programmes of the HPV vaccines in January 2018—which included 206 comparative studies—and this information was subsequently forwarded to the Cochrane review authors. However, given that almost half of the trials and participants were missing from the Cochrane review findings, its conclusion that there was a small risk of reporting bias "was inappropriate", said Dr Jørgensen and his colleagues.

All of the 26 trials considered by the Cochrane review authors compared the HPV vaccine with active comparators (e.g. adjuvants, hepatitis vaccines), but these were mistakenly referred to as placebo. Dr Jørgensen and his colleagues commented that "the use of active comparators probably increased the occurrence of harms in the comparator groups and thereby masked harms caused by the HPV vaccines".

13.1 No confidence in findings

Dr Jørgensen and his colleagues also lacked confidence in the Cochrane review conclusions regarding the risk of serious AEs associated with HPV vaccines, and the assumed risks for control groups. One such example was that although more deaths occurred in the HPV vaccine groups versus comparator groups (51 vs 39), this was dismissed as a chance finding by the Cochrane review authors. However, Dr Jørgensen and his colleagues indicated that the recorded deaths may have been coded in a way that does not raise suspicion that the HPV vaccine may have caused the deaths. Comparatively, they noted VigiBase records (as of May 2018) revealed 499 deaths reportedly associated with HPV vaccination.

Dr Jørgensen and his colleagues concluded that the Cochrane review should not be considered as "trusted evidence" given that it was influenced by reporting bias and biased trial designs. They recommended that the Cochrane review authors should "make every effort to identify all trials and their limitations and conduct reviews accordingly".

Jorgensen L, Gotzsche PC, Tom Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. BMJ Evidence-Based Medicine. Epub 27 Jul 2018. https://doi.org/10.1136/bmjebm-2018-111012. Accessed 19 Sep 2018.

14 MHRA Encourages Suspected ADR Reporting During Pregnancy

Suspected ADRs associated with medicines taken during pregnancy (in the mother and/or offspring) should be reported via the Yellow Card Scheme, says the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

The agency highlighted that medicines should only be taken during pregnancy unless absolutely necessary and that "obstetricians and midwives have a particularly important role in providing data about pregnancy outcomes", as they can provide key information such as prenatal scan results and background information regarding a pregnancy.

The MHRA added that "we are concerned that underreporting in this important area may lead to missing drug safety signals, including miscarriage, congenital anomalies, or developmental disorders".

Yellow Cards may be submitted by patients, caregivers or healthcare professionals when they suspect that an adverse reaction or abnormal pregnancy outcome is related to a medicine taken during pregnancy. "It is important to provide as much information as possible in relation to the suspected adverse reaction in the mother or child", noted the MHRA.

The agency outlined some of the information it would like to receive (where available), including:

- last menstrual period and expected delivery date if the pregnancy is ongoing, and dates when the suspected medicine was taken;
- other medicines and/or vaccines taken during pregnancy (including folic acid, herbal medicines and/or any medicine obtained without a prescription), with dates;
- information regarding if the mother has undergone her 20-week scan;
- details of any maternal medical history (or current maternal medical condition) relevant to the pregnancy (including details of in vitro fertilisation conception and antenatal scans, or any other significant events during the pregnancy);
- information regarding any delivery complications (e.g. emergency caesarean section, fetal distress, or other complications in the baby);
- details of any previous pregnancies and outcomes; and
- sufficient contact information that will allow for subsequent follow-up by the MHRA if more detailed information is required.

Medicines and Healthcare products Regulatory Agency (UK). Medicines taken during pregnancy: please report suspected adverse drug reactions, including in the baby or child, on a Yellow Card. Drug Safety Update 2018;11(12):8–10.

15 Call for Collaboration on Prices of Orphan Drugs

Following a discussion on orphan drug pricing at the Second International Workshop on Orphan Drugs, participants are calling for collaboration on prices of orphan drugs, say authors of a Viewpoint published in the *Lancet*.

The Orphan Drugs Act aimed at facilitating and incentivising the development of drugs for rare diseases and disorders was signed in the US in 1983, and similar legislation for orphan medicinal products (OMP) was passed by the European Commission in 2000. However, the increasing number of OMPs being introduced each year for over 7000 rare diseases is threatening the sustainability of healthcare systems.

In the UK, the National Institute for Health and Care Excellence (NICE) values drugs based on a willingness-to-pay threshold in terms of cost per quality-adjusted life-year (QALY) gained. The adaptive pathway approach to valuing drugs has been explored in the EU but has not yet been adopted. Use of patient registries collecting reliable longitudinal data from doctors appears to be the best way to assess the value of orphan drugs in real life, according to the authors. Production costs must be considered in valuing drugs, but when research on a new drug is done primarily by academics through public funding, costs for research and development may be reduced.

Ever increasing drug costs have led to concerns in healthcare systems throughout the world, and corrective measures including restrictions on indications for the use of drugs, risk sharing, payments based on performance, and monitoring the appropriate use of drugs, have helped to limit drug expenditure. However, incentives for orphan drugs should continue, in order to encourage drug companies to develop more OMPs.

"We think the price proposed by the industry must be subject to scrutiny and regulation," said the authors. They listed the following criteria for assessing the value of a new OMP: the incidence or prevalence of the disease, disease severity, and knowledge regarding disease aetiology, pathogenesis and pathophysiology; manufacturer-related costs for previous research and development, production costs related to complexity, costs of previous drug failures, and profit margins; and patient benefits (life-saving, life-changing, effects on quality of life [QOL], other treatments available or unmet need, and certainty regarding disease modification).

A drug requiring further investigation could receive early market access associated with a robust evaluation system, at a reduced price that can subsequently be adjusted after use of the drug is optimised, the authors suggested. If an OMP becomes indicated for a non-rare disease, the drug price should be reduced as marketing for the other disease increases.

The authors believe there is a need for new legislation in Europe, and suggest three key recommendations for pricing of OMPs: price negotiations should be Europe-wide, not within member states; pricing should be based on research and development costs plus production costs, and the value of the drug with respect to patient life and QOL; and pricing should allow for drug company profits (with higher prices per patient when the target population is smaller), and "European legislation on OMPs should include new rules, which might include effectiveness-related payments and should be monitored by the Antitrust Authority".

"Following these recommendations would be a logical way to redress the balance between the profit that industry naturally expects and the costs that health services can bear," they said.

Luzzatto L, Hyry HI, Schieppati A, et al. Outrageous prices of orphan drugs: a call for collaboration. Lancet 2018;392(10149):791–4.

16 Slow Adoption of Biosimilars by UK Prescribers

Adoption of biosimilars (generic equivalents of biological drugs) by prescribers in the UK is slow despite their lower costs, according to authors of an editorial published in the *BMJ*.

Biosimilars are approved by regulatory authorities and must be highly similar to originator drugs in terms of pharmacodynamics and pharmacokinetics, and have comparable efficacy and safety. Guidance by the UK NICE and the US FDA recommends biosimilars when appropriate, and the WHO plans to prequalify biosimilars for cancer therapy so that they are eligible for procurement by United Nations agencies. A systematic review of 58 studies found that potential cost savings achieved by switching from originator biologics to biosimilars outweighed the risks of harms.

The authors reviewed data from OpenPrescribing.net on prescribing in general practices (GPs) in England, and from the NHS Medicines Optimisation Dashboard, to assess prescribing rates of biosimilars. Insulin glargine is the only biosimilar commonly prescribed in primary care in England. Originator insulin glargine (Lantus) accounted for 90% of insulin glargine prescribing by GPs. The biosimilar (Abasaglar) accounted for only 60% of new prescriptions for insulin glargine from the time it was licensed, indicating that 40% of new patients were prescribed Lantus despite its NHS price being 7% higher than for the biosimilar. Prescribing information on three biosimilars was available on the Medicines Optimisation Dashboard; in January 2018, biosimilars accounted for 76% of etanercept prescribing, 90% of infliximab prescribing and only 60% of rituximab prescribing.

"When a biosimilar has been licensed, there should be no concerns about starting treatment with it rather than the originator. And switching to a cheaper product in a patient who is already taking an originator can also be recommended when there is high quality evidence of equivalence of the benefits and harms, provided progress is carefully monitored," said the authors.

Aronson JK, Goldacre B, Ferner RE. Prescribing biosimilars. BMJ 2018;362:k3141.

17 Approaches to Increasing Affordability of Drugs

A report on approaches to increasing the affordability of drugs in the US has been published by CVS Health. The company has announced that CVS Caremark will adopt techniques used by other pharmacy benefit managers (PBMs) in an attempt to curb the cost of drugs.

CVS currently employs three strategies to improve the affordability of drugs: encouraging treatment with lower-cost drugs including generic drugs through step therapy; utilising prior authorisation of drugs to ensure appropriate evidence-based use; and allowing competition between clinically equivalent drugs to determine which drugs will be listed on the formulary. However, CVS will introduce three new strategies: providing assistance to patients in the deductible phase of health insurance; using comparative effectiveness to reduce launch prices of new drugs; and providing transparency to enable members and pharmacists to understand the true costs of prescribed treatment.

If clients make use of point-of-sale rebates and use the CVS Caremark Standard Formulary, CVS expects to implement zero copayments for drugs for chronic diseases including asthma, chronic obstructive pulmonary disease, depression, diabetes mellitus, hyperlipidaemia and hypertension.

Of note, CVS Caremark's new program will allow clients to exclude from their plan any drug launched at a cost exceeding $100 000 per QALY gained, as determined by the Institute for Clinical and Economic Review (ICER), with the exception of drugs considered breakthrough therapies by the US FDA.

"No one but manufacturers have, until now, had any control over the launch price of newly patented drugs. This new approach, harnessing the power of the market, could change manufacturer behavior," said CVS Health.

CVS Health. Current and new approaches to making drugs more affordable. 2018 Aug [online]. Available from URL: https://cvshealth.com/sites/default/files/cvs-health-current-and-new-approaches-to-making-drugs-more-affordable.pdf. Accessed 19 Sep 2018.

18 NICE Call for Evidence on CAR-T Therapy

NICE has put out a call for feedback on an innovative treatment for aggressive subtypes of non-Hodgkin lymphoma, which could influence its availability on the NHS, after draft guidance recommended against it.

Axicabtagene ciloleucel (Yescarta, Kite Pharma) has shown promise in the treatment of diffuse large, and primary mediastinal B-cell lymphoma, but at more than £50 000 per QALY gained, compared with the current standard of care, could not be considered cost effective for the NHS.

The drug is the first chimeric antigen receptor T-Cell (CAR-T) therapy, personalised for each patient using their own white blood cells, reengineered to recognise and attack their cancer cells. Approximately 4800 people per year have these lymphomas in the UK, and there is no current survival-improving treatment.

The Director of the NICE Centre for Health Technology Evaluation, Meindert Boysen, said "CAR-T is an exciting innovation in very difficult to treat cancers, with a promise of cure for some patients". He also said "Although promising, there is still much more we need to know about CAR-T, and unfortunately, in this case, we are not able to recommend axicabtagene ciloleucel for use in the NHS in England at the cost per patient set by Kite Pharma".

National Institute for Health and Care Excellence. Feedback encouraged to allow use of life extending treatment on NHS for those with blood cancer. 2018 Aug 28 [online]. Available from URL: https://www.nice.org.uk/news/article/feedback-encouraged-to-allow-use-of-life-extending-treatment-on-nhs-for-those-with-blood-cancer. Accessed 19 Sep 2018.

19 More News from ICER

In August 2018 the US ICER posted a Draft Scoping Document on AVXS 101 and nusinersen for spinal muscular atrophy (SMA), a Draft Evidence Report on four treatments for the prevention of hereditary angioedema attacks, an Evidence Report on antiandrogens for nonmetastatic castration-resistant prostate cancer, and an Evidence Report on inotersen and patisiran for amyloidosis [1–4].

19.1 AVXS 101 and Nusinersen for SMA

ICER posted a Draft Scoping Document on its planned review on the value of AVXS 101 (AveX) and nusinersen (Spinraza; Biogen) for the treatment of SMA.

Nusinersen was approved by the US FDA for treatment of SMA in children and adults in 2016, and an FDA decision on treatment with AVXS 101 in infants with SMA is expected in the first quarter of 2019.

The draft scoping document was open for public comment until 7 September 2018, and a revised scoping document is expected to be posted on 19 September. ICER's report on these therapies will be the subject of a meeting of the New England Comparative Effectiveness Public Advisory Council (CEPAC) in March 2019.

19.2 Therapies for Hereditary Angioedema

ICER released a Draft Evidence Report assessing the effectiveness and value of four therapies for long-term prophylaxis against hereditary angioedema attacks, including lanadelumab (Takhzyro; Shire), and three complement C1 inhibitors: Cinryze (Shire), Haegarda (CSL Behring) and Ruconest (Pharming).

Lanadelumab was approved by the US FDA for the prevention of hereditary angioedema in August 2018.

The draft report will be open for public comment until 20 September 2018. Comments and any necessary changes in the Evidence Report and Revised Voting Questions are expected to be posted on 11 October, and the report will be subject of a public meeting of the California Technology Assessment Forum (CTAF) on 25 October 2018.

19.3 Antiandrogens for Prostate Cancer

ICER released an Evidence Report assessing the effectiveness and value of three antiandrogen therapies for nonmetastatic castration-resistant prostate cancer: abiraterone (Zytiga; Janssen Biotech) apalutamide (Erleada; Janssen Biotech) and enzalutamide (Xtandi; Astellas Pharma). Sun Pharma's formulation of abiraterone (Yonsa) was not evaluated.

Evidence showed a net health benefit with apalutamide or enzalutamide compared with androgen deprivation therapy (ADT) alone, but less certainty that abiraterone in combination with prednisone achieved a net health benefit versus ADT alone. Estimated incremental cost-effectiveness ratios for apalutamide and enzalutamide versus ADT were within accepted willingness-to-pay thresholds of $50 000–$150 000 per QALY gained. However, at current net prices, with typical rebates and discounts from wholesale acquisition cost, only approximately 19% and 18% of eligible patients could be treated with apalutamide or enzalutamide, respectively, before reaching the potential budget impact threshold of $991 million per year.

"Unfortunately, the lack of long-term survival data and the absence of head-to-head trials limits our ability to compare the effectiveness of enzalutamide with that of the newer drug apalutamide. For abiraterone, we have less certainty in its added benefits when used before cancer progression is detected, making it even more difficult to judge how its effectiveness matches up with the other treatment options. However, for all three drugs, while there are additional costs associated with earlier treatment, those costs appear to be aligned with the clinical benefits patients receive," said Dr David Reid, Chief Medical Officer at ICER.

This Evidence Report was the subject of a public meeting of the Midwest CEPAC on 13 September 2018.

19.4 Inotersen and Patisiran for Amyloidosis

ICER also released an Evidence Report assessing the effectiveness and value of inotersen (Tegsedi; Akcea Therapeutics) and patisiran (Onpattro; Alnylam Pharmaceuticals) for treatment of hereditary transthyretin (hATTR) amyloidosis. This Evidence Report was also the subject of the public meeting of the Midwest CEPAC on 13 September 2018.

Patisiran has been recently approved by the FDA, and an approval decision on inotersen is expected in October 2018.

Evidence on the clinical effectiveness of inotersen and patisiran indicated that they "offer important advancements for patients with hATTR amyloidosis," said Dan Ollendorf, Chief Scientific Officer at ICER. "However, the announced price of patisiran, even taking into account expected discounts, far exceeds commonly cited cost-effectiveness thresholds. During our public meeting, the Midwest CEPAC will discuss evidence on these therapies with a policy roundtable of experts, working to identify policy solutions to ensure appropriate patient access despite the extremely high costs. We are hopeful that inotersen's manufacturer takes the report and meeting discussions under consideration when setting its price," he said.

To date, there have been no studies comparing inotersen and patisiran, but evidence showed that inotersen provided a small or substantial health benefit compared with best supportive care, and patisiran provided at least a small net health benefit compared with best supportive care.

Economic evaluations of the long-term cost-effectiveness of patisiran versus best supportive care found that at a net price of $345 000, the incremental cost-effectiveness ratio (ICER) was $850 000 per QALY gained, which far exceeded willingness-to-pay thresholds of $50 000–$150 000 per QALY gained. The list price of patisiran would need to be discounted by 90%–95% to align costs with added benefits. The list price of inotersen has not yet been announced, but ICERs suggest that it would be cost effective at a price of $15 300–$25 400 per year.

1. Institute for Clinical and Economic Review. Institute for Clinical and Economic Review posts draft scoping document on AVXS-101 and nusinersen for spinal muscular atrophy. 2018 Aug 22 [online]. Available from URL: https://icer-review.org/announcements/institute-for-clinical-and-economic-review-posts-draft-scoping-document-on-avxs-101-and-nusinersen-for-spinal-muscular-atrophy. Accessed 19 Sep 2018.
2. Institute for Clinical and Economic Review. Institute for Clinical and Economic Review releases draft evidence report on long-term treatments for prevention of hereditary angioedema attacks. 2018 Aug 23 [online]. Available from URL: https://icer-review.org/announcements/hae-draft-report. Accessed 19 Sep 2018.

3. Institute for Clinical and Economic Review. Institute for Clinical and Economic review report finds evidence inadequate to distinguish the clinical benefits of different antiandrogen therapies for men with nonmetastatic castration-resistant prostate cancer. 2018 Aug 24 [online]. Available from URL: https://icer-review.org/announcements/prostate-cancer-evidence-report. Accessed 19 Sep 2018.
4. Institute for Clinical and Economic Review. Institute for Clinical and Economic review finds current list price of patisiran for amyloidosis far exceeds standard cost-effectiveness levels. 2018 Aug 29 [online]. Available from URL: https://icer-review.org/announcements/amyloidosis-evidence-report. Accessed 19 Sep 2018.

20 Are Patients with Migraine Willing to Pay for Monoclonal Antibodies?

Tertiary private settings with a defined willingness to pay may represent the best option for using monoclonal antibodies for the treatment of patients with migraine in Brazil, report researchers from that country.

The researchers used a questionnaire involving 53 patients with episodes of migraine, treated at the Headache Centre of Rio de Janeiro, to evaluate satisfaction with their current treatment. The patients' knowledge about upcoming monoclonal antibodies for migraine treatment and their willingness to pay for these agents were also assessed. The study was conducted in November and December 2017.

The results of the study, presented at the 60th Annual Scientific Meeting of the American Headache Society, showed that 62% of the patients were not at all or only slightly satisfied with their daily preventive medications. Nearly 42% indicated they would switch to an injectable medication if it was shown to be more effective than their current medication and not to be used daily, even if it was associated with much higher cost. Nearly 53% reported they were willing to pay up to $R500 (approximately $US156) per month for such a medication, and nearly 23% were willing to pay up to $R1000 (approximately $US312) per month.

Jevoux C, Krymchantowski AV. Monoclonal antibodies (mAb) for migraine and willingness to pay in a tertiary center [abstract no PF69]. 60th Annual Scientific Meeting of the American Headache Society. June 28–July 1, 2018; San Franscisco, CA, USA. Available from URL: https://americanheadachesociety.org/events/60th-annual-scientific-meeting. Accessed 19 Sep 2018.

21 Emerging Issues of Differential Pricing of Drugs

Differential pricing of drugs across countries based on gross domestic product (GDP) per capita appears to be a potentially efficient strategy that could enable wider access to drugs in low and middle income countries (LMICs), compared with uniform pricing across markets, but issues have emerged with regard to differential pricing, says Professor Patricia Danzon from the University of Pennsylvania in an article published in *PharmacoEconomics*.

Value-based differential pricing theory incorporates insurance coverage and addresses static and dynamic efficiency. However, limited empirical evidence indicates a weak positive relationship between drug prices and GDP per capita, and differential pricing is undermined by external referencing and parallel trade, says the author.

Factors that undermine differential pricing in practice include: the high growth in drug prices in the US relative to GDP, leading to widening differentials between the US and other high-income countries with different insurance and payer strategies; concerns over the effects of confidential rebates; and the growth of branded generics in LMICs leading to complex markets with both product and price differentiation.

Differential pricing across countries based roughly on GDP is most easily implemented in countries with a universal national or social insurance system where a single regulator reflects public preferences and the willingness-to-pay for health. However, in countries with pluralistic payers, confidential rebating off a list price can theoretically achieve competitive, differential pricing between payers but if list prices are not constrained and rebates passed through to payers, rebating may contribute to higher list prices and distorted prescribing incentives, commented the author. In LMICs where most patients pay out-of-pocket for drugs, differential pricing appears to lead to the use of lower-priced, branded generics, yielding a differential products and pricing outcome that increases access, utilisation and static efficiency, with little effect on dynamic efficiency, she said.

Danzon PM. Differential pricing of pharmaceuticals: theory, evidence and emerging issues. Pharmacoeconomics. Epub 30 Jul 2018. https://doi.org/10.1007/s40273-018-0696-4. Accessed 19 Sep 2018.

22 Health Canada: Risk of Acute Pancreatitis with SGLT2 Inhibitors

There appears to be a link between use of sodium-glucose transporter-2 (SGLT2) inhibitors and the potential risk of acute pancreatitis, says Health Canada.

This class of prescription drugs is approved in Canada for use in adults with type 2 diabetes mellitus. Health Canada reviewed the potential risk of both acute and chronic pancreatitis with SGLT2 inhibitors after Canadian case reports and those published in the scientific literature indicated there could be a possible link.

For the Canadian case reports, the agency received 20 reports of acute pancreatitis associated with SGLT2 inhibitors, but there were no reports of chronic pancreatitis. Of these, only one report met the review criteria and was further assessed—demonstrating a possible link between the use of SGLT2 inhibitors and acute pancreatitis.

"The review also looked at 476 international reports and 6 published cases of pancreatitis related to the use of SGLT2 inhibitors", added Health Canada. Of these, only 28 cases of acute pancreatitis were further assessed—18 of which demonstrated a possible link to use of a SGLT2 inhibitor. No cases of chronic pancreatitis met the review criteria. The agency added that other medical conditions and medicines could have caused the pancreatitis in most of the remaining case reports.

"A review of the scientific literature did not find any published studies that showed an increased risk of pancreatitis in patients treated with SGLT2 inhibitors", added Health Canada.

The agency noted that it is working with manufacturers of SGLT2 inhibitor products to update the respective safety information to include this pancreatitis risk; this information is not included in the product safety information in the US or EU.

Government of Canada. Summary safety review—SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin)—Health Canada. 2018 Jul 20 [online]. Available from URL: https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00204. Accessed 19 Sep 2018.

23 POMME Cohort Valuable Tool to Assess Prenatal Drug Exposure

The French PrescriptiOn Médicaments Mères Enfants (POMME) cohort is a valuable tool to assess the long-term effects of prenatal exposure to medicines—particularly psychomotor development, say French researchers.

Implemented in July 2010, the POMME cohort comprises routinely collected data from: (i) the French Health Insurance Database (i.e. medicines and medical care prescriptions and reimbursements to children and mothers during pregnancy); and (ii) the Mother and Child Protection Centre Database (i.e. child health certificates at birth, 9 months, and 24 months of age).

Children born in a region of south-west France over a 1-year period are registered in POMME every 5 years. Each 5-year period forms a different cohort for comparative use (i.e. POMME 2010, POMME 2015).

To date, 8372 children have been recorded in POMME. Although these children have reached 7 years of age, 2018 data have not yet been collected and so the participant characteristics presented in this article concerned children until 6 years of age.

In utero, children had been exposed to a mean of 9.8 ± 6.1 medicines, and drug exposure was greatest in children aged 0–2 years. After 2 years of age, the number of drugs prescribed and reimbursed to children gradually decreased.

Overall, 908 children (10.8%) presented with ≥ 2 signs of psychomotor development disorders.

The researchers noted that "medicines for the digestive system were the most commonly used during intrauterine life (82.3% of the children exposed in utero), and in newborns (74.8%)".

Paracetamol was the most commonly used drug during antenatal life (65.1%) and during childhood (99.3%). During antenatal life, other commonly used drugs included phloroglucinol (42.9%), amoxicillin (28.8), sodium bicarbonate, helicidine and sodium alginate (all approximately 22%). During childhood, other commonly used drugs were ibuprofen (90.7%), amoxicillin (90.2%), colecalciferol (89.8%) and lidocaine (87.6%).

The researchers concluded that "recording these data would make it possible to assess the risk of the long-term consequences of prenatal medicine exposure".

Benevent J, Hurault-Delarue C, Araujo M et al. POMME: the new cohort to evaluate long-term effects after prenatal medicine exposure. Drug Saf. Epub 19 Aug 2018. https://doi.org/10.1007/s40264-018-0712-9. Accessed 19 Sep 2018.

24 SGLT-2 Inhibitors Increase Risk of Amputation in T2DM

Treatment with SGLT-2 inhibitors in patients with type 2 diabetes mellitus (T2DM) appears to increase the risk of amputation compared with other oral antihyperglycaemics, according to findings of a retrospective study published in *JAMA Internal Medicine* [1].

US Truven Health MarketScan Commercial Claims and Encounters data from September 2012 to September 2015 were used to investigate the risk of foot or leg amputation, critical limb ischaemia, osteomyelitis, peripheral arterial disorders and vascular ulcers in 39 869 patients with T2DM who were new users of SGLT-2 inhibitors, 105 023 new users of CD26 antigen inhibitors [DPP-4 inhibitors], 39 120 new users of glucogen-like peptide 1 stimulants [GLP-1 agonists], and 769 894 new users of older antihyperglycaemics (metformin, sulfonylureas or thiazolidinediones).

After adjustment for propensity score, severity of diabetes, demographical parameters, comorbid diseases and other treatments, there was a small increase in the risk of amputation with new use of SGLT-2 inhibitors compared

with CD26 antigen inhibitors (adjusted hazard ratio [aHR] 1.50; 95% CI 0.85, 2.67) and GLP-1 agonists (aHR 1.47; 95% CI 0.64, 3.36), and a significantly increased risk compared with use of the older antihyperglycaemics (aHR 2.12; 95% CI 1.19, 3.77).

New users of SLGT-2 inhibitors also had significantly increased rates of osteomyelitis, peripheral vascular disease and vascular ulcers compaared with new users of the older antihyperglycaemics.

"The FDA has recently placed a boxed warning on products containing canagliflozin; however, regulators have not issued statements on whether this association is a class-wide association," noted the authors. "Given the uncertainty regarding the true nature of the association between SLGT-2 inhibitors and amputation, clinicians and patients will have to navigate treatment choices while balancing the potential risks of these products against their benefits and alternatives." they said.

The increased risk of amputation was first reported in the Canagliflozin Cardiovascular Assessment Study (CANVAS), in which "patients randomized to receive canagliflozin had a nearly 2-fold increased risk of lower limb amputation compared with those who received placebo," said Dr Michael Fischer from Brigham and Women's Hospital, Harvard Medical School, and colleagues in an invited commentary published in *JAMA Internal Medicine* [2]. "The study by Chang et al helps to contextualize the risk in a relatively low-risk patient population, but does not settle the debate . . . Until more data are available, the results of CANVAS provide the greatest evidence that canagliflozin is associated with an increased risk of amputation and should influence our prescribing accordingly," they commented.

1. Chang HY, Singh S, Mansour O, et al. Association between sodium-glucose cotransporter 2 inhibitors and lower extremity amputation among patients with type 2 diabetes. JAMA Intern Med 2018;178(9):1190–8.
2. Fralick M, Patorno E, Fischer MA. Sodium-glucose cotransporter 2 inhibitors and the risk of amputation: results and challenges from the real world. JAMA Intern Med 2018;178(9):1199–1200.

25 Bullous Pemphigoid with Diabetes Medications?

Treatment with dipeptidyl pepdidase-4 inhibitors (DPP-4i) has been association with an increased risk of bullous pemphigoid (BP). According to study results reported in the *Journal of the American Academy of Dermatology*, there does not seem to be an association between BP and other oral diabetes medications, "indicating they can be safely used in this population".

The retrospective study used the Finnish Care Register in 1997–2013 to identify 3397 patients with BP. After matching with 12 941 controls who had basal cell carcinoma, drugs used by both groups were identified using the Social Insurance Institution of Finland database.

There were 4524 patients with diabetes in the BP group, including 887 identified with type 2 diabetes mellitus (19.6%). Of the 66 138 controls with diabetes, 8111 controls had type 2 diabetes mellitus (12.3%).

At least one evaluated diabetes medication had been used by 582 patients with BP (17.1%) and 1555 controls (12.0%). There was no association between any of the medications, whether individually or as a drug class, and an increased risk of BP, including sulfonylureas, thiazolidinediones, metformin combined with thiazolidinediones. The authors note that the association with glucagon-like peptide-1 (GLP-1) receptor agonists could not be evaluated "due to few patients using these medications".

"Our results suggest that other classes of oral antidiabetics can be used as a substitute for DPP-4i without risk of further aggravating BP symptoms", note the authors, who add that "generalization of these results to other populations will require further studies".

Varpuluoma O, Forsti AK, Jokelainen J, et al. Oral diabetes medications other than dipeptidyl peptidase-4 inhibitors are not associated with bullous pemphigoid: a Finnish nationwide case control study. J Am Acad Dermatol. Epub 24 May 2018. https://doi.org/10.1016/j.jaad.2018.05.030. Accessed 19 Sep 2018.

26 Haemorrhage with CYP450-Inducing Anticonvulsants

The risk of maternal or neonatal bleeding complications does not appear to increase following the use of CYP450-inducing anticonvulsants (ACDi) during late pregnancy, according to study results reported in *Neurology*, which provides "some reassurance with regard to hemorrhagic complications for clinicians and pregnant women".

The population-based cohort study used the Medicaid Analytic eXtract database in 2000–2010 to identify pregnant women who delivered a liveborn infant. The 5109 women who filled an ACDi prescription (i.e. for carbamazepine, oxcarbazepine, phenobarbital, phenytoin, topiramate) with a drug supply that overlapped their delivery date were compared to 6463 women receiving other ACDs. Results were propensity-score adjusted using > 50 variables.

Postpartum haemorrhage (PPH) was diagnosed in 135 ACDi recipients and 231 other ACD recipients (2.6% vs 3.6%; adjusted relative risk [RR] 0.77; 95% CI 0.58, 1.00). Neonatal bleeding occurred in 157 ACDi recipients and 229 other ACD recipients (3.1% vs 3.5%; RR 0.83; 0.64,

1.08). The most frequent events were intraventricular haemorrhage (35 vs 44 patients) and cutaneous haemorrhage (34 vs 58 patients). Results were similar in sensitivity analyses.

Evaluation of a negative control, with the ACD supply ending > 1 month before delivery and an assumption of no carry-over, did not result in "meaningful differences" from the main analysis (RR 0.66 for PPH and RR 0.85 for neonatal haemorrhage), but the authors note that "the similar protective association observed could suggest residual confounding by unmeasured characteristics". They conclude that "our findings suggest that use of ACDi in late pregnancy does not meaningfully increase the risks of bleeding complications including PPH and neonatal bleeding complications in clinical settings where neonatal intramuscular vitamin K administration is considered standard of care".

Panchaud A, Cohen JM, Patorno E, et al. Anticonvulsants and the risk of perinatal bleeding complications: A pregnancy cohort study. Neurology 2018;91(6):e533–e542.

27 Safety of Antidepressants After TBI Assessed in Older Adults

Older adults hospitalised for traumatic brain injury (TBI) do not appear to have an increased risk of AEs, according to US researchers.

TBI is a significant health problem in the US (particularly among older adults) and resulting neuropsychiatric disorders are common. However, there is poor evidence supporting the use of any pharmacological treatment for such TBI-related neuropsychiatric disorders.

Medicare administrative claims data were analysed for almost 31 000 eligible older beneficiaries (average age 79.7 years) who were hospitalised with TBI between 2006 and 2010, and their monthly use of the three most commonly used classes of antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs] and tricyclic antidepressants [TCAs]) was assessed.

SSRIs were the most commonly used class of antidepressants (23%), followed by SNRIs (5%) and TCAs (3%).

In total, just over 23 000 AEs were observed—with ischaemic stroke (36%) being the most common of the six AEs evaluated, followed by fracture (22.5%). In contrast, haemorrhagic stroke and seizures were the two least common AEs observed (7.4% and 7.99%, respectively).

In addition, users of SSRIs had an almost 2.5-times higher risk of haemorrhagic stroke versus users of TCAs, but no other antidepressant class comparisons were associated with an increased risk of AEs.

The researchers noted that healthcare providers can utilise these results to guide appropriate selection of antidepressant treatment for use in older adults following TBI.

Albrecht JS, Rao V, Perfetto EM, et al. Safety of antidepressant classes used following traumatic brain injury among Medicare beneficiaries: a retrospective cohort study. Drugs Aging 2018;35(8):763–72.

28 Skin Reactions Linked with PD-1 Inhibitors can be Delayed

Skin reactions associated with use of programmed cell death protein-1 (PD-1) inhibitors can be delayed onsets and can also occur after treatment discontinuation, according to a retrospective US study.

Researchers from Perelman School of Medicine at the University of Pennsylvania examined the timing of cutaneous immune-related adverse reactions (irAEs) in 17 patients (12 men and 5 women) with diverse biopsy-proven cutaneous irAEs following treatment with a PD-1 inhibitor (i.e. pembrolizumab, nivolumab or nivolumab + concomitant ipilimumab).

Five patients developed cutaneous irAEs within 3 months of treatment initiation, but the majority of patients (n = 12; 71%) developed these reactions ≥ 3 months of starting treatment with pembrolizumab or nivolumab. The cutaneous irAEs observed included eczema, lupus-like reaction, lichenoid dermatitis, bullous pemphigoid, erythema multiforme, and sarcoidosis.

The time from treatment initiation to skin reaction onset ranged from 0.5–38.0 months (median 4.2 months).

The researchers highlighted that the cutaneous irAEs associated with PD-1 inhibitor therapy actually developed after the drug was stopped in five cases. Therefore, they urge dermatologists to be aware of the potential for delayed presentations of such cutaneous irAEs.

Wang LL, Patel G, Chiesa-Fuxench ZC, et al. Timing of onset of adverse cutaneous reactions associated with programmed cell death protein 1 inhibitor therapy. JAMA Dermatol 2018;154(9):1057–61.

29 Ovarian Insufficiency Not Linked to Adolescent Vaccinations

There is no significantly increased risk of primary ovarian insufficiency (POI) following adolescent vaccinations, according to a US-based population study.

Utilising Kaiser Permanente Northwest electronic health records, researchers retrospectively assessed a cohort of almost 200 000 female patients aged 11–34 years who received human papillomavirus (HPV) vaccination (received by > 58 800 patients), or other recommended adolescent

vaccinations including diphtheria, tetanus and acellular pertussis (DTaP) vaccination (received by > 119 000 patients), meningococcal vaccine groups A, C, Y, W-135 conjugate (MenACWY) vaccination (> 46 200 patients), and inactivated influenza vaccination (received by > 84 700 patients) for diagnoses suggestive of POI.

A total of 46 confirmed, idiopathic POI cases were confirmed (33 probable cases, 13 possible cases). The study researchers noted that "the incidence of diagnosed POI increased with age, from a low of 0.87 per 1 000 000 person-months in 11- to 14-year-olds to a peak of 12.85 per 1 000 000 person-months in 30- to 34-year-olds". The median time from symptom onset to POI diagnosis was 3 years in this cohort.

In addition, the researchers noted that one patient (16-year-old girl) with POI had received HPV vaccination 23 months before symptom onset (primary menorrhoea) and the first clinical evaluation for delayed menarche—which was not consistent with other published cases that reported POI onset with 12 months of vaccination.

The adjusted hazard ratio (HR) of POI was 0.30 (95% CI 0.07, 1.36) after HPV vaccination, 0.88 (95% CI 0.37, 2.10) after DTaP vaccination, 1.42 (95% CI 0.59, 3.41) after inactivated influenza vaccination, and 0.94 (95% CI 0.27, 3.23) after MenACWY vaccination.

The researchers concluded that "we believe this study should lessen concern surrounding potential impact on fertility from HPV or other adolescent vaccination".

Naleway AL, Mittendorf KF, Irving SA, et al. Primary ovarian insufficiency and adolescent vaccination. Pediatrics 2018;142(3): e20180943.

30 New Warning on Label of Neuromuscular Blockers

The Australian TGA is introducing a mandatory warning label on the packaging of neuromuscular blocking agents (atracurium, cisatracurium, mivacurium, pancuronium, rocuronium, suxamethonium and vecuronium) to warn of the risk of serious AEs.

Medication administration errors during use of neuromuscular blocking agents in patients undergoing anaesthesia is associated with a risk of paralysis, respiratory arrest, severe permanent physical or psychological harm, and death. These errors may be due to look-alike packaging, resulting in the wrong drug being administered.

To minimise look-alike medicine selection errors, the TGA is introducing mandatory warning statements on the container and outer packaging of neuromuscular blocking agents, such as "WARNING: Paralysing agent". The warnings must be in black text on a red background. Companies must introduce warnings to their labels and sell out old stock by September 2020. Since neuromuscular blocking agents are only available in hospitals for administration by healthcare professionals, patients are not expected to see the new labelling, noted the TGA.

Therapeutic Goods Administration. New warnings on labels of medicines containing neuromuscular blocking agents. 2018 Jun 29 [online]. Available from URL: https://www.tga.gov.au/new-warnings-labels-medicines-containing-neuromuscular-blocking-agents. Accessed 19 Sep 2018.