NEWSLETTER

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Thromb Haemost 2019;119(2):319-327. doi: 10.1055/s-0038-1676611.

CHARACTERISTICS AND MANAGEMENT OF PATIENTS WITH VENOUS THROMBOEMBOLISM: THE GARFIELD-VTE REGISTRY.

Ageno W, Haas S, Weitz JI, Goldhaber SZ, Turpie AGG, Goto S, Angchaisuksiri P, Nielsen JD, Kayani G, Pieper KS, Schellong S, Bounameaux H, Mantovani LG, Prandoni P, Kakkar AK; GARFIELD-VTE investigators.

Background: Management of venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), varies worldwide.

Methods: The Global Anticoagulant Registry in the FIELD - Venous Thromboembolism (GARFIELD-VTE) is a prospective, observational study of 10,685 patients with objectively diagnosed VTE recruited from May 2014 to January 2017 at 417 sites in 28 countries. All patients are followed for at least 3 years. We describe the baseline characteristics of the study population and their management within 30 days of diagnosis.

Results: The median age was 60.2 years; 50.4% were male; 61.7% had DVT and 38.3% had PE ± DVT; and 32.3% were obese (body mass index ≥ 30 kg/m2). The most common risk factors were surgery (12.5%), hospitalization (12.0%) and trauma to the lower limbs (7.8%). At the time of VTE diagnosis, 10.1% had active cancer and 5.7% were chronically immobilized. Treatment for VTE was anticoagulant (AC) therapy alone in 90.9% of patients; 5.1% received thrombolytic and/or surgical/mechanical therapy ± AC and 4.0% received no therapy. Pre-diagnosis, 12.8% received AC therapy alone and 0.2% received thrombolytic and/or surgical/mechanical therapy ± AC. After diagnosis, parenteral AC therapy alone was administered in 17.6% of patients, and it was followed by a direct oral AC (DOAC) in 16.4% or a vitamin K antagonist (VKA) in 26.8%. DOACs alone were prescribed to 32.3% of patients, while 5.9% received VKA alone.

Conclusions: The initial findings from this global registry highlight the heterogeneity in characteristics and management of VTE patients. Prospective follow-up will reveal the impact of this heterogeneity on outcomes.

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Mult Scler 2018:1352458518799598. doi: 10.1177/1352458518799598.

LIVER INJURY WITH DRUGS USED FOR MULTIPLE SCLEROSIS: A CONTEMPORARY ANALYSIS OF THE FDA ADVERSE EVENT REPORTING SYSTEM.

Antonazzo IC, Poluzzi E, Forcesi E, Riise T, Bjornevik K, Baldin E, Muratori L, De Ponti F, Raschi E.

Background: Drug-induced liver injury (DILI) has been observed in patients with multiple sclerosis (MS), raising concerns on the liver safety of MS drugs.

Objective: To describe DILI events with MS drugs by analyzing the FDA Adverse Event Reporting System.
Methods: DILI reports were extracted and classified in overall liver injury (OLI), including asymptomatic elevation of liver enzymes, and severe liver injury (SLI). We performed disproportionality analysis by calculating adjusted reporting odds ratios (RORs) with 95% confidence interval (CI) and case-by-case evaluation for concomitant drugs with hepatotoxic potential.
Results: Fampridine showed statistically significant ROR for both OLI and SLI, whereas teriflunomide and fingolimod generated solid disproportionality (ROR > 2) only for OLI (ROR, 2.31; 95% CI, 2.12-2.52; and 2.53; 2.40-2.66, respectively). Among monoclonal antibodies, only alemtuzumab generated higher-than-expected ROR for OLI (1.34; 1.09-1.65). We also detected the expected hepatotoxic potential of beta interferon and mitoxantrone. Concomitant reporting of hepatotoxic drugs ranged from 26% (dimethyl fumarate) to 90% (mitoxantrone).
Conclusions: These real-world pharmacovigilance findings suggest that DILI might be a common feature of MS drugs and call for (1) formal population-based study to verify the risk of fampridine and (2) awareness by clinicians, who should assess the possible responsibility of MS drugs when they diagnose DILI.

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Circulation 2019;139(6):787-798. doi: 10.1161/CIRCULATIONAHA.118.035012.

EARLY RISKS OF DEATH, STROKE/SYSTEMIC EMBOLISM, AND MAJOR BLEEDING IN PATIENTS WITH NEWLY DIAGNOSED ATRIAL FIBRILLATION.

Bassand JP, Virdone S, Goldhaber SZ, Camm AJ, Fitzmaurice DA, Fox KAA, Goto S, Haas S, Hacke W, Kayani G, Mantovani LG, Misselwitz F, Pieper KS, Turpie AGG, van Eickels M, Verheugt FWA, Kakkar AK.

Background: Atrial fibrillation is associated with increased risks of death, stroke/systemic embolism, and bleeding (incurred by antithrombotic therapy), which may occur early after diagnosis.
Methods: We assessed the risk of early events (death, stroke/systemic embolism, and major bleeding) over 12 months and their relation to the time after diagnosis of atrial fibrillation in 52 014 patients prospectively enrolled in the GARFIELD-AF registry (Global Anticoagulant Registry in the FIELD-Atrial Fibrillation) between March 2010 and August 2016.
Results: Over 12 months, 2140 patients died (mortality rate, 4.3; 95% CI, 4.2-4.5 per 100 person-years), of whom 288 (13.5%) died in the first month (6.8; 95% CI, 6.1-7.6). Over 12 months, 657 patients had a stroke/systemic embolism (1.3; 95% CI, 1.2-1.4) and 411 had a major bleeding (0.8; 95% CI, 0.8-0.9). During the first month, the rates (per 100 person-years) of stroke/systemic embolism and major bleed were 2.3 (95% CI, 1.9-2.8) and 1.5

(95% CI, 1.2-1.9), respectively. The elevated 1-month mortality rate was mostly attributable to cardiovascular mortality (3.5; 95% CI, 3.0-4.1), in particular, heart failure, sudden death, and acute coronary syndromes (1.0 [95% CI, 0.8-1.4], 0.6 [95% CI, 0.4-0.8], and 0.5 [95% CI, 0.3-0.8], respectively). Age, heart failure, prior stroke, history of cirrhosis, vascular disease, moderate-to-severe kidney disease, diabetes mellitus, and living in North or Latin America were independent predictors of a higher risk of early death, whereas anticoagulation and living in Europe or Asia were independent predictors of a lower risk of early death. A predictive model developed for the 1-month risk of death had a C-statistic of 0.81 (95% CI, 0.78-0.83).
Conclusions: The increased hazard of early events, in particular, cardiovascular mortality, in newly diagnosed atrial fibrillation points to the importance of comprehensive care for such patients and should alert clinicians to detect warning signs of possible early mortality.

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Front Pharmacol 2019;9:1543. doi: 10.3389/fphar.2018.01543.

Galenic Preparations of Therapeutic Cannabis sativa Differ in Cannabinoids Concentration: A Quantitative Analysis of Variability and Possible Clinical Implications.

Bettiol A, Lombardi N, Crescioli G, Maggini V, Gallo E, Mugelli A, Firenzuoli F, Baronti R, Vannacci A.

Introduction: Magistral preparations of therapeutic cannabis are extracted from standardized products imported from Holland or from the Florence Military Pharmaceutical Chemical Works, but extraction protocols differ among galenic laboratories. This study assessed the inter-laboratory variability in concentrations of cannabidiol (CBD), cannabinol (CBN), tetrahydrocannabinol (THC), and tetrahydrocannabinolic acid (THCA) among different magistral oil preparations.
Methods: 219 samples of Bediol, Bedrobinol, Bedrolite or FM-2 70 or 100 mg/ml in oil were collected from 3 laboratories. Concentrations of CBD, CBN, THC, and THCA were quantified by high-pressure liquid chromatography; inter-laboratories variability was assessed using the Kruskal-Wallis test.
Results: A significant variability in CBD and THC concentrations was found for Bediol 70 mg/ml samples from 2 laboratories [for CBD: median 5.4 (range 4.8-6.6) vs. 6.1 (4.9-7.2) mg/ml, p = 0.033; for THC: 3.6 (3.1-3.9) vs. 4.0 (2.6-5.1) mg/ml, p = 0.020]. As for Bediol 100 mg/ml, a significant variability emerged in THC concentrations among the three considered laboratories [5.7 (-) vs. 4.2 (1.5-4.8) vs. 5.2 (4.2-6.9), p = 0.030]. No significant inter-laboratory variability emerged for Bedrocan and Bedrolite. Concentrations of CBD, CBN, and THC were <LOQ in all Bedrocan samples, and CBN and THCA were <LOQ in

all Bedrolite samples. As for FM-2, a significant inter-laboratories variability was found for CBD concentrations.
Conclusions: Quantitative variability of cannabinoids in magistral preparations might impact on the efficacy and safety of therapeutic cannabis. A standardized protocol is needed to guarantee a homogeneous product and patients' therapeutic continuity.

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Evid Based Complement Alternat Med 2018;2018:1035875. doi: 10.1155/2018/1035875.

THE IMPACT OF PREVIOUS PREGNANCY LOSS ON LACTATING BEHAVIORS AND USE OF HERBAL MEDICINES DURING BREASTFEEDING: A POST HOC ANALYSIS OF THE HERBAL SUPPLEMENTS IN BREASTFEEDING INVESTIGATION (HABIT).

Bettiol A, Lombardi N, Marconi E, Crescioli G, Bonaiuti R, Maggini V, Gallo E, Mugelli A, Firenzuoli F, Ravaldi C, Vannacci A.

Introduction: Complementary and alternative medicines (CAMs) are commonly used among lactating women, despite the poor knowledge of these products and of their safety. Perception of pregnancy- and breastfeeding-related difficulties and consequent use of CAMs may differ in bereaved women, by force of the distress related to previous loss, although no literature evidence is available. This Herbal supplements in Breastfeeding InvesTigation (HaBIT) post hoc analysis explored the impact of previous pregnancy loss on lactating behaviors and on use of CAMs during breastfeeding.
Methods: A web-based survey was conducted among lactating women with no previous alive child, resident in Tuscany (Italy). Data on lactating behavior and on CAMs use were collected and evaluated among women with previous pregnancy loss as compared to control women.
Results: Out of 476 women answering the questionnaire, 233 lactating women with one child were considered. Of them, 80 had history of pregnancy loss. Cesarean birth was significantly more frequent among women with history of pregnancy loss as compared to controls (41% versus 22%; p=0.004). Proportion, length of exclusive breastfeeding, and occurrence of breastfeeding-related complications were comparable among the two cohorts. More than half of women used CAMs during breastfeeding. Use of CAMs was more frequent among women with previous pregnancy loss (54% versus 68%; p=0.050), specifically considering herbal preparations (16% versus 30%; p=0.018). Major advisors for CAMs use were midwives. 18% and 23% of women without and with history of pregnancy loss declared no clear perception on CAMs efficacy and safety.
Conclusions: Overcoming the social taboo of pregnancy loss and training healthcare professionals for an adequate management of the perinatal period are essential for an effective and safe care. Despite the common use and advice on CAMs use during breastfeeding, it is important to acknowledge that limited evidence supports their safety and efficacy during such critical period.

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Eur J Pediatr 2019;178(2):161-172. doi: 10.1007/s00431-018-3281-0.

CENTRAL NERVOUS SYSTEM-ACTIVE DRUG ABUSED AND OVERDOSE IN CHILDREN: A WORLDWIDE EXPLORATORY STUDY USING THE WHO PHARMACOVIGILANCE DATABASE.

Carnovale C, Mahzar F, Scibelli S, Gentili M, Arzenton E, Moretti U, Leoni O, Pozzi M, Peeters GGAM, Clementi E, Medaglia M, Radice S.

Recent epidemiological studies have reported an increase in central nervous system (CNS)-active drug abuse rates in paediatric settings, raising several public health concerns. No study to date has explored this issue worldwide. We performed an extensive analysis of drugs abuse/overdose reported for children in the last decade by using the largest pharmacovigilance database, i.e. the VigiBase, collecting adverse drug reaction reports that involved at least one suspect drug belonging to the Anatomical Therapeutic Chemical code "Nervous System" through the Standardised Medical Dictionary for Drug Regulatory Affairs Queries for Drug abuse. 8.682 reports matched our criteria. An increase in reporting activity was observed, starting from 2014; an intentional overdose was reported more frequently than an accidental one, with a difference between age groups. We retrieved 997 reports with death outcome. These referred more to adolescents (n = 538) than subjects of any other paediatric age group. Paracetamol and opioid analgesics were the most common suspect drugs in deaths across all age groups due to hypoxic-ischaemic encephalopathy, brain death, and cardio-respiratory arrest.Conclusion: The number of reports associated with drug abuse and overdose is increasing (for opioid and paracetamol-containing products) and a considerable number of adverse drug reactions are serious. Data on the patterns of use of such medicines from each country may help in implementing strategies of risk-minimisation and renewing healthcare recommendations worldwide. An increased clinical awareness of drug abuse and overdose is warranted, while continuing to provide effective treatments. What is Known: • The large increase in paediatric prescriptions for CNS-active drugs in the last 20 years has recently raised public health concerns about drug abuse and overdose. • No study to date has examined this issue in paediatric patients worldwide. What is New: • The number of paediatric reports associated with CNS drug abuse and intentional overdose is increasing, including those with fatal outcome; over 4 years; more than 35% of the reports was entered from European countries. • Opioid and paracetamol were most frequently suspected for ADRs with fatal outcome across all age groups, due to hypoxic-ischaemic encephalopathy and cardio-respiratory arrest, suggesting the need to implement strategies of risk-minimisation.

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BMJ Paediatr Open 2018; 2(1):e000334. doi: 10.1136/bmjpo-2018-000334.

SPIROMETRY MONITORING IN ASTHMATIC CHILDREN IN LOMBARDY REGION, ITALY.

Casartelli P, Clavenna A, Cartabia M, Bortolotti A, Fortino I, Merlino L, Biondi A, Bonati M.

Objectives: To evaluate the diagnostic and therapeutic approaches in a cohort of asthmatic children before and after starting drug therapy.

Methods: Data were retrieved from administrative databases of the Lombardy Region. The study population was composed of 78 184 children born in the Lombardy Region in 2002 and followed until their 10th birthday. Children with at least one antiasthmatic drug prescription per year (with the exclusion of nebulised suspension/solution formulations) in 2 consecutive years and at least one antiasthmatic drug prescription after the fifth birthday were identified as potential asthmatics (PA). Each PA was monitored for a period starting from 12 months before and ending 24 months after the first prescription (index prescription, IP). During the monitoring period antiasthmatic drug prescriptions were analysed, as well as spirometry and/or specialist visits.

Results: A total of 59 975 children (76.7%) received >/=1 prescription of antiasthmatic drugs in their first 10 years of life, and 4475 (5.7%) were identified as PAs. In all, 24% of PAs started with short-acting beta2-agonists (SABA), 23% with inhaled corticosteroids (ICS) and 20% with SABA+ICS.A total of 33% of PAs had at least one prescription for specialist visit/spirometry: 11% before and 28% after the IP. The factors associated with a greater likelihood of receiving visit/spirometry prescriptions were local health unit of residence, age and high use of asthma drugs.

Conclusions: Despite international guideline recommendations, spirometry monitoring is still underused in asthmatic children, even in subjects who initiated pharmacological treatment and therefore need an airway function evaluation. Moreover, the choice of drug therapy appears not always rational, since one out of four children were commenced on ICS as monotherapy.

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Eur J Prev Cardiol 2018 Nov 26: 2047487318814970. doi: 10.1177/2047487318814970.

PATTERNS OF TREATMENT WITH ANTIPLATELET THERAPY AFTER AN ACUTE CORONARY SYNDROME: DATA FROM A LARGE DATABASE IN A COMMUNITY SETTING.

Cimminiello C, Dondi L, Pedrini A, Ronconi G, Calabria S, Piccinni C, Polo Friz H, Martini N, Maggioni AP.

Aims: Current guidelines strongly recommend antiplatelet therapy with aspirin plus a $P2Y_{12}$ receptor inhibitor (dual therapy) for patients with acute coronary syndrome (ACS). To better understand how antiplatelet treatment is prescribed in clinical practice, the aim of this study was to provide a more detailed description of real-world patients with and

without antiplatelet treatment after an ACS, their outcomes at one-year follow-up and the related integrated cost.
Methods: The ReS database, including more than 12 million inhabitants, was evaluated. During the accrual period ACS patients discharged alive were identified on the basis of ICD-IX-CM code. Antiplatelet drug prescriptions and healthcare costs were analysed over one-year follow-up.
Results: In 2014, of the 25,129 patients discharged alive after an ACS, 5796 (23%) did not receive any antiplatelet therapy during the first month after hospital discharge. Among them, 3846 (66%) subjects were prescribed an antiplatelet drug subsequently, while 7.7% did not receive any antiplatelet treatment during the whole following year. Dual therapy in the subgroup of patients undergoing a revascularization procedure (n = 8436) was prescribed to 79.2% of cases and to 46.1% (n = 4009) of medically managed patients. The patients not treated with an antiplatelet treatment in the first month showed the highest one-year healthcare costs, mostly due to hospital re-admissions.
Conclusions: This analysis of a large patient community shows that a considerable proportion of patients remained untreated with antiplatelet treatment after an ACS event. A clearer characterization of these subjects can help to improve the adherence to the current guidelines and recommendations.

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J Biomed Inform 2018;84:184-199. doi: 10.1016/j.jbi.2018.07.001.

FROM NARRATIVE DESCRIPTIONS TO MEDDRA: AUTOMAGICALLY ENCODING ADVERSE DRUG REACTIONS.

Combi C, Zorzi M, Pozzani G, Moretti U, Arzenton E.

Context: The collection of narrative spontaneous reports is an irreplaceable source for the prompt detection of suspected adverse drug reactions (ADRs). In such task qualified domain experts manually revise a huge amount of narrative descriptions and then encode texts according to MedDRA standard terminology. The manual annotation of narrative documents with medical terminology is a subtle and expensive task, since the number of reports is growing up day-by-day.
Objectives: Natural Language Processing (NLP) applications can support the work of people responsible for pharmacovigilance. Our objective is to develop NLP algorithms and tools for the detection of ADR clinical terminology. Efficient applications can concretely improve the quality of the experts' revisions. NLP software can quickly analyze narrative texts and offer an encoding (i.e., a list of MedDRA terms) that the expert has to revise and validate.
Methods: MagiCoder, an NLP algorithm, is proposed for the automatic encoding of free-text descriptions into MedDRA terms. MagiCoder procedure is efficient in terms of computational complexity. We tested MagiCoder through several experiments. In the

first one, we tested it on a large dataset of about 4500 manually revised reports, by performing an automated comparison between human and MagiCoder encoding. Moreover, we tested MagiCoder on a set of about 1800 reports, manually revised ex novo by some experts of the domain, who also compared automatic solutions with the gold reference standard. We also provide two initial experiments with reports written in English, giving a first evidence of the robustness of MagiCoder w.r.t. the change of the language.
Results: For the current base version of MagiCoder, we measured an average recall and precision of 86.9% and 91.8%, respectively.
Conclusions: From a practical point of view, MagiCoder reduces the time required for encoding ADR reports. Pharmacologists have only to review and validate the MedDRA terms proposed by the application, instead of choosing the right terms among the 70 K low level terms of MedDRA. Such improvement in the efficiency of pharmacologists' work has a relevant impact also on the quality of the subsequent data analysis. We developed MagiCoder for the Italian pharmacovigilance language. However, our proposal is based on a general approach, not depending on the considered language nor the term dictionary.

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IEEE J Biomed Health Inform 2019;23(1):95-102. doi: 10.1109/JBHI.2018.2861213.
NORMALIZING SPONTANEOUS REPORTS INTO MEDDRA: SOME EXPERIMENTS WITH MAGICODER.

Combi C, Zorzi M, Pozzani G, Arzenton E, Moretti U.

Text normalization into medical dictionaries is useful to support clinical tasks. A typical setting is pharmacovigilance (PV). The manual detection of suspected adverse drug reactions (ADRs) in narrative reports is time consuming and natural language processing (NLP) provides a concrete help to PV experts. In this paper, we carry out experiments for testing performances of MagiCoder, an NLP application designed to extract MedDRA terms from narrative clinical text. Given a narrative description, MagiCoder proposes an automatic encoding. The pharmacologist reviews, (possibly) corrects, and then, validates the solution. This drastically reduces the time needed for the validation of reports with respect to a completely manual encoding. In previous work, we mainly tested MagiCoder performances on Italian written spontaneous reports. In this paper, we include some new features, change the experiment design, and carry on more tests about MagiCoder. Moreover, we do a change of language, moving to English documents. In particular, we tested MagiCoder on the CADEC dataset, a corpus of manually annotated posts about ADRs collected from the social media.

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J Clin Med 2019;8(1). pii: E81. doi: 10.3390/jcm8010081.

SEX-DIFFERENCES IN THE PATTERN OF COMORBIDITIES, FUNCTIONAL INDEPENDENCE, AND MORTALITY IN ELDERLY INPATIENTS: EVIDENCE FROM THE REPOSI REGISTER.

Corrao S, Argano C, Natoli G, Nobili A, Corazza GR, Mannucci PM, Perticone F; REPOSI Investigators.

Background: The RePoSi study has provided data on comorbidities, polypharmacy, and sex dimorphism in hospitalised elderly patients.

Methods: We retrospectively analysed data collected from the 2010, 2012, 2014, and 2016 data sets of the RePoSi register. The aim of this study was to explore the sex-differences and to validate the multivariate model in the entire dataset with an expanded follow-up at 1 year.

Results: Among 4714 patients, 51% were women and 49% were men. The disease distribution showed that diabetes, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and malignancy were more frequent in men but that hypertension, anaemia, osteoarthritis, depression, and diverticulitis disease were more common in women. Severity and comorbidity indexes according to the Cumulative Illness Rating Scale (CIRS-s and CIRS-c) were higher in men, while cognitive impairment, mood disorders, and disability in daily life measured by the Barthel Index (BI) were worse in women. In the multivariate analysis, BI, CIRS, and malignancy significantly increased the risk of death in men at the 1-year follow-up, while age was independently associated with mortality in women.

Conclusions: Our study highlighted the relevance and the validity of our previous predictive model in the identification of sex dimorphism in hospitalised elderly patients underscoring the need of sex-personalised health-care.

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Int J Clin Pharm 2018;40(4):744-747. doi: 10.1007/s11096-018-0657-1.

AN HISTORICAL OVERVIEW OVER PHARMACOVIGILANCE.

Fornasier G, Francescon S, Leone R, Baldo P.

Pharmacovigilance started about 170 years ago, although it was not yet named as such at that time. It is structured activity in the professional health field, with important social and commercial implications aimed at monitoring the risk/benefit ratio of drugs, improving patient's safety and the quality of life. In this commentary we report the milestones of pharmacovigilance up to the present day, in order to understand all the steps that have characterized the historical evolution; from the first reports, which were essentially letters or warnings sent by clinicians to publishers of important and famous scientific journals, up to today's modern and ultra-structured electronic registries. The historical phases also help us to understand why pharmacovigilance helped us to achieve

such important results for man's health and for pharmacology itself, and to identify the challenges that await Pharmacovigilance in future years.

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Expert Opin Drug Metab Toxicol 2018;14(10):1057-1069. doi: 10.1080/17425255.2018.1530213.

PHARMACOKINETICS OF NEW ORAL ANTICOAGULANTS: IMPLICATIONS FOR USE IN ROUTINE CARE.

Ingrasciotta Y, Crisafulli S, Pizzimenti V, Marcianò I, Mancuso A, Andò G, Corrao S, Capranzano P, Trifirò G.

Since 2008, new oral anticoagulants (NOACs) have been approved for the prevention of venous thromboembolism (VTE) in patients receiving hip or knee replacement surgery, prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), treatment of deep vein thrombosis (DVT), and pulmonary embolism (PE). Premarketing randomized clinical trials (RCTs) of NOACs demonstrated their non-inferiority in terms of efficacy vs. warfarin (traditional oral anticoagulant - TOA), with lower risk of serious adverse drug reactions, especially cerebral hemorrhages. In clinical practice, pharmacokinetic aspects of NOACs have to be carefully taken into account to optimize the benefit-risk profile of these drugs. Areas covered: An overview of major issues related to pharmacokinetics of NOACs, such as drug-drug interactions, over- and underdosage in special populations (e.g. elderly, underweight, and chronic kidney disease patients), and impact on adherence and persistence to NOACs therapy and ultimately clinical outcomes in real-world setting, is provided. Expert opinion: NOACs have been proven to be a better option than traditional anticoagulants due to better tolerability and ease of use. However, given specific pharmacokinetic characteristics, NOAC therapy has to be carefully tailored and monitored in relation to patient characteristics with the final goal of maximizing benefits and minimizing risks.

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Eur J Intern Med 2018 Dec 4. pii: S0953-6205(18)30448-5. doi: 10.1016/j.ejim.2018.11.003.

MORTALITY RATE AND RISK FACTORS FOR GASTROINTESTINAL BLEEDING IN ELDERLY PATIENTS.

Lenti MV, Pasina L, Cococcia S, Cortesi L, Miceli E, Caccia Dominioni C, Pisati M, Mengoli C, Perticone F, Nobili A, Di Sabatino A, Corazza GR; REPOSI Investigators.

Background: Gastrointestinal bleeding (GIB) is burdened by high mortality rate that increases with aging. Elderly patients may be exposed to multiple risk factors for GIB. We aimed at defining the impact of GIB in elderly patients.

Methods: Since 2008, samples of elderly patients (age ≥ 65 years) with multimorbidity admitted to 101 internal medicine wards across Italy have been prospectively enrolled and followed-up (REPOSI registry). Diagnoses of GIB, length of stay (LOS), mortality rate, and possible risk factors, including drugs, index of comorbidity (Cumulative Illness Rating Scale [CIRS]), polypharmacy, and chronic diseases were assessed. Adjusted multivariate logistic regression models were computed.
Results: 3872 patients were included (mean age 79 ± 7.5 years, F:M ratio 1.1:1). GIB was reported in 120 patients (mean age 79.6 ± 7.3 years, F:M 0.9:1), with a crude prevalence of 3.1%. Upper GIB occurred in 72 patients (mean age 79.3 ± 7.6 years, F:M 0.8:1), lower GIB in 51 patients (mean age 79.4 ± 7.1 years, F:M 0.9:1), and both upper/lower GIB in 3 patients. Hemorrhagic gastritis/duodenitis and colonic diverticular disease were the most common causes. The LOS of patients with GIB was 11.7 ± 8.1 days, with a 3.3% in-hospital and a 9.4% 3-month mortality rates. Liver cirrhosis (OR 5.64; CI 2.51-12.65), non-ASA antiplatelet agents (OR 2.70; CI 1.23-5.90), and CIRS index of comorbidity >3 (OR 2.41; CI 1.16-4.98) were associated with GIB ($p < 0.05$).
Conclusions: A high index of comorbidity is associated with high odds of GIB in elderly patients. The use of non-ASA antiplatelet agents should be discussed in patients with multimorbidity.

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BMC Cancer 2019;19(1):113. doi: 10.1186/s12885-019-5310-4.

OPIOID RESPONSE IN PAEDIATRIC CANCER PATIENTS AND THE VAL158MET POLYMORPHISM OF THE HUMAN CATECHOL-O-METHYLTRANSFERASE (COMT) GENE: AN ITALIAN STUDY ON 87 CANCER CHILDREN AND A SYSTEMATIC REVIEW.

Lucenteforte E, Vannacci A, Crescioli G, Lombardi N, Vagnoli L, Giunti L, Cetica V, Coniglio ML, Pugi A, Bonaiuti R, Aricò M, Giglio S, Messeri A, Barale R, Giovannelli L, Mugelli A, Maggini V.

Background: Genetic polymorphisms in genes involved in pain modulation have been reported to be associated to opioid efficacy and safety in different clinical settings.
Methods: The association between COMT Val158Met polymorphism (rs4680) and the inter-individual differences in the response to opioid analgesic therapy was investigated in a cohort of 87 Italian paediatric patients receiving opioids for cancer pain (STOP Pain study). Furthermore, a systematic review of the association between opioid response in cancer patients and the COMT polymorphism was performed in accordance with the Cochrane Handbook and the Prisma Statement.
Results: In the 87 paediatric patients, pain intensity (total time needed to reach the lowest possible level) was significantly higher for G/G than A/G and A/A carriers (p-value = 0.042). In the 60 patients treated only with morphine, the mean of total dose to reach the same pain intensity was significantly higher for G/G than A/G and A/A carriers

(p-value = 0.010). Systematic review identified five studies on adults, reporting that opioid dose (mg after 24 h of treatment from the first pain measurement) was higher for G/G compared to A/G and A/A carriers.
Conclusions: Present research suggests that the A allele in COMT polymorphism could be a marker of opioid sensitivity in paediatric cancer patients (STOP Pain), as well as in adults (Systematic Review), indicating that the polymorphism impact could be not age-dependent in the cancer pain context.

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Eur Heart J Acute Cardiovasc Care 2018 Sep 13: 2048872618801252. doi: 10.1177/2048872618801252.

THE USE OF ANTIPLATELET AGENTS AFTER AN ACUTE CORONARY SYNDROME IN A LARGE COMMUNITY ITALIAN SETTING OF MORE THAN 12 MILLION SUBJECTS.

Maggioni AP, Dondi L, Pedrini A, Ronconi G, Calabria S, Cimminiello C, Martini N.

Background: Antiplatelet agents are the cornerstone of medical treatment in acute coronary syndromes. The aim of this study was to evaluate the clinical epidemiology of patients after an acute coronary syndrome treated with different antiplatelet agent regimens in a large real community setting.
Methods: The ARCO database, including more than 12 million inhabitants, was evaluated. Antiplatelet agent prescriptions were analysed as follows: aspirin, clopidogrel, other antiplatelet agents used alone; the free and fixed combination of clopidogrel and aspirin; the free combination of aspirin with other antiplatelet agents. Healthcare costs included drug prescriptions (prices reimbursed by the Italian National Health System), outpatient specialist services and hospitalisations (Italian national tariffs).
Results: From 1 January to 31 December 2014, 26,834 patients were discharged after an acute coronary syndrome. Of these, 19,333 (77%) were prescribed with an antiplatelet agent. Among patients undergoing a revascularisation procedure either percutaneous or surgical (47% of the total population), antiplatelet agents were prescribed in 90% of cases. Dual antiplatelet agent therapy was prescribed in 49.6% of the total population and in 68.5% of those treated invasively. Prescription continuity was observed in just 75% of patients. The highest adherence was observed for the fixed combination of aspirin/clopidogrel (81.5%). Throughout one year of follow-up re-hospitalisation occurred in 47.9% of the patients and the direct cost per patient treated with an antiplatelet agent was €13,297 versus €16,647 in patients not treated with antiplatelet agents.
Conclusions: This study highlights that antiplatelet agent prescriptions, specifically dual antiplatelet agent therapy, are at least suboptimal as well as in prescription continuity.

Hospitalisations were frequent and were the main driver of the costs, accounting for 84% of the total costs for the Italian National Health System.

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Eur J Intern Med 2018 Oct 18. pii: S0953-6205(18)30395-9. doi: 10.1016/j.ejim.2018.10.002.

HEALTHCARE RESOURCE USE IN XALIA: A SUBGROUP ANALYSIS OF A NON-INTERVENTIONAL STUDY OF RIVAROXABAN VERSUS STANDARD ANTICOAGULATION FOR DEEP VEIN THROMBOSIS.

Mantovani LG, Haas S, Kreutz R, Folkerts K, Gebel M, Monje D, Schneider J, van Eickels M, Sahin K, Zell E, Ageno W, Turpie AGG.

Introduction: The non-interventional XALIA study compared the safety and effectiveness of rivaroxaban with standard anticoagulation for the treatment of venous thromboembolism in routine clinical practice. This substudy assessed the effect of treatment with rivaroxaban on healthcare resource use, hospital length of stay (LOS) and frequency of hospitalisation.

Methods: n XALIA, patients aged ≥18 years scheduled to receive ≥3 months of rivaroxaban or standard anticoagulation treatment for deep vein thrombosis (DVT) were eligible. Treatment decisions were at the physician's discretion. Healthcare resource use, including hospital admission for the index DVT and initial LOS, was documented. The main analyses in this substudy were conducted in a 1:1 propensity score-matched set (PMS) of patients, with adjustment for cancer at baseline.

Results: In the PMS analysis, 1124 rivaroxaban-treated patients and 1124 standard anticoagulation-treated patients were included. Baseline characteristics were similar between groups (mean age 60.8 years vs. 61.2 years, DVT only rates of 89.7% vs. 90.2% and cancer rates of 8.4% vs. 8.5%, respectively). Of these, 433/1124 (38.5%) rivaroxaban-treated patients and 438/1124 (39.0%) standard anticoagulation-treated patients were hospitalised. Index event LOS in the PMS analysis was a least-squares mean of 2.6 days shorter with rivaroxaban vs. standard anticoagulation (5.4 vs. 8.0 days; geometric means ratio = 0.67 [95% confidence interval 0.61-0.74, P < 0.001]).

Conclusions: In XALIA, hospital LOS was shorter with rivaroxaban than with standard anticoagulation, consistent with the phase III study results. DVT treatment with rivaroxaban in routine clinical practice may reduce the cost per patient vs. standard anticoagulation.

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Curr Med Res Opin 2018 Oct 25:1-6. doi: 10.1080/03007995.2018.1541315.

PRESCRIBING PATTERNS OF ALLOPURINOL AND FEBUXOSTAT ACCORDING TO DIRECTIVES ON THE REIMBURSEMENT CRITERIA AND CLINICAL GUIDELINES: ANALYSIS OF A PRIMARY CARE DATABASE.

Marconi E, Bettiol A, Lombardi N, Crescioli G, Parretti L, Vannacci A, Medea G, Cricelli C, Lapi F.

Objective: According to American clinical guidelines, allopurinol and febuxostat may be prescribed as first-line therapy to treat hyperuricemia. However, the Italian Medicines Agency directive, called Nota 91, allows the reimbursement of second-line febuxostat in the case of failure and/or intolerance of a previous allopurinol therapy, so partially embracing European League Against Rheumatism recommendations and the British Society for Rheumatology Guideline. Such inconsistency might lead to heterogeneity among General Practitioners (GPs) in treatment of hyperuricemia. This study, therefore, aimed to evaluate the prescribing behavior of GPs in terms of compliance with Nota 91 and/or official guidelines.

Methods: Using the Health Search Database, a retrospective cohort study was conducted to evaluate the patterns of use of allopurinol and febuxostat between 2011 and 2016.

Results: In total, 44,257 and 5837 patients were prescribed with allopurinol and febuxostat, respectively. Among febuxostat users, 4321 (74%) had a previous allopurinol treatment; 92% of switches to febuxostat were related to hyperuricemia, whereas 9% of switchers presented intolerance to allopurinol; 26% of patients were prescribed with febuxostat as first-line therapy. The presence of diabetes and/or moderate/severe renal disease were statistically significant determinants of febuxostat use as first-line therapy.

Conclusions: Prescriptions of febuxostat were highly compliant to Nota 91. Only a sub-group of frontline prescriptions of febuxostat were mainly driven by the presence of renal dysfunction, which is able to increase the risk of allopurinol intolerance and/or inefficacy. These findings indicate that GPs' prescribing behavior for hyperuricemia is highly compliant with both regulatory directives and clinical guidelines.

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Int J Cardiol 2018;273:183-186. doi: 10.1016/j.ijcard.2018.09.054.

MYOCARDITIS AND PERICARDITIS AFTER IMMUNIZATION: GAINING INSIGHTS THROUGH THE VACCINE ADVERSE EVENT REPORTING SYSTEM.

Mei R, Raschi E, Forcesi E, Diemberger I, De Ponti F, Poluzzi E.

Aim: To characterize cases of myocarditis (MC) and pericarditis (PC) recorded in the Vaccine Adverse Event Reporting System (VAERS).

Methods: Cases were extracted from VAERS (2011–2015) and assessed for causality using standardized WHO algorithm. Disproportionality analysis was performed through reporting odds ratio (ROR) with 95%CI. MEDLINE was also searched.

Results: In VAERS, 199 cases of MC or PC were collected, among which 149 reported smallpox vaccine. The remaining were: 15 cases in 'YOUNGER GROUP' (YG; <18 years old) and 35 in 'OLDER GROUP' (OG; >18 years old). Main reported vaccines were against Human Papilloma Virus (n = 6) in YG and influenza (n = 16) in OG. Causality always resulted "undeterminate" for YG, whereas either "undetermined" (30 cases) and "correlated" (3 cases) for OG. Statistically significant ROR was found in YG for meningococcal vaccine (ROR = 3.55; 95%CI = 1.23–10.24) and in OG for thyphoid vaccine (11.13; 7.73–16.03), Japanese encephalitis vaccine (8.54; 2.7–27.01), anthrax (25.5; 18.8–34.5), and, as expected, smallpox (71.88; 49.25–104.89). In MEDLINE, 91 articles were found: positive/possible causality was frequently reported.
Conclusions: MC and PC after immunization appear extremely rare; only in very few cases can a role of vaccine be actually identified. Signals for vaccines against typhus, Japanese encephalitis, anthrax and meningococcus warrant monitoring.

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Lancet 2018;392(10145):383-384. doi: 10.1016/S0140-6736(18)31557-5.

REPORTING OF IMMUNE CHECKPOINT INHIBITOR-ASSOCIATED MYOCARDITIS.

Noseda R, Magro L, Stathis A, Ceschi A.

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Drugs Aging 2019;36(1):85-91. doi: 10.1007/s40266-018-0612-9.

RELATION BETWEEN DELIRIUM AND ANTICHOLINERGIC DRUG BURDEN IN A COHORT OF HOSPITALIZED OLDER PATIENTS: AN OBSERVATIONAL STUDY.

Pasina L, Colzani L, Cortesi L, Tettamanti M, Zambon A, Nobili A, Mazzone A, Mazzola P, Annoni G, Bellelli G.

Background: Delirium is a neuropsychiatric syndrome which occurs on average in one out of five hospitalized older patients. It is associated with a number of negative outcomes, including worsening of cognitive and functional status, increasing the burden on patients and caregivers, and elevated mortality. Medications with anticholinergic effect have been associated with the clinical severity of delirium symptoms in older medical inpatients, but this association is still debated.
Objective: The aim was to assess the association between delirium and anticholinergic load according to the hypothesis that the cumulative anticholinergic burden increases the risk of delirium.
Methods: This retrospective, cross-sectional study was conducted in a sample of older patients admitted to the Acute Geriatric Unit (AGU) of the San Gerardo Hospital in Monza (Italy) between June 2014 and January 2015. Delirium was diagnosed on admission using the 4 'A's Test (4AT), a validated screening tool for delirium diagnosis,

which has shown good sensitivity and specificity to detect this condition in elderly patients admitted to an AGU. Each patient's anticholinergic burden was measured with the Anticholinergic Cognitive Burden (ACB) scale, a ranking of anticholinergic medications to predict the risk of adverse effects on the central nervous system in older patients.
Results: Of the 477 eligible for the analysis, 151 (31.7%) had delirium. According to the ACB scale, 377 patients (79.0%) received at least one anticholinergic drug. Apart from quetiapine, which has a strong anticholinergic effect, the most commonly prescribed anticholinergic medications had potential anticholinergic effects but unknown clinically relevant cognitive effects according to the ACB scale (score 1). Patients with delirium had a higher anticholinergic burden than those without delirium, with a dose-effect relationship between total ACB score and delirium, which was significant at univariate analysis. A plateau risk was found in patients who scored 0-2, but patients who scored 3 or more had about three or six times the risk of delirium than those not taking anticholinergic drugs. The dose-response relationship was maintained in the multivariate model adjusted for age and sex [odds ratio (OR) 5.88, 95% confidence interval (CI) 2.10-16.60, p = 0.00007], while there was only a non-significant trend in the models adjusted also for dementia and Mini Nutritional Assessment (OR 2.73, 95% CI 0.85-8.77, p = 0.12).
Conclusions: Anticholinergic drugs may influence the development of delirium due to the cumulative effect of multiple medications with modest antimuscarinic activity. However, this effect was no longer evident in multivariable logistic regression analysis, after adjustment for dementia and malnutrition. Larger, multicenter studies are required to clarify the complex relationship between drugs, anticholinergic burden and delirium in various categories of hospitalized older patients, including those with dementia and malnutrition.

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Epilepsy Behav 2018; 92:14-17. doi: 10.1016/j.yebeh.2018.09.033.

PERINATAL OUTCOME AND HEALTHCARE RESOURCE UTILIZATION IN THE FIRST YEAR OF LIFE AFTER ANTIEPILEPTIC EXPOSURE DURING PREGNANCY.

Putignano D, Clavenna A, Campi R, Canevini MP, Vignoli A, Battino D, Beghi E, Perucca E, Bortolotti A, Fortino I, Merlino L, Bonati M.

Healthcare administrative databases of Italy's Lombardy Region were analyzed with the aim to assess perinatal outcomes and healthcare resource utilization during the first year of life in infants exposed to antiepileptic drugs (AEDs) during pregnancy. Drug prescriptions dispensed in the 12months before delivery to women, who delivered between 2005 and 2011, were analyzed. Neonates were classified as cases if exposed to AEDs, and each case was randomly matched to seven controls. No significant differences were observed in the risk of congenital malformations between 526 cases and 3682

controls except for valproic acid (odds ratio (OR): 2.29; 95% confidence interval (CI): 1.24-4.22) where cases were more likely to be small for gestational age (chi(2)=7.66; p=0.006). Cases also had a higher probability than controls of needing at least one specialist visit in a child neuropsychiatry outpatient service (OR: 1.74; 95% CI: 1.22-2.49).

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Expert Opin Pharmacother 2018;19(17):1903-1914. doi: 10.1080/14656566.2018.1531126.

PHARMACOTHERAPY OF TYPE 2 DIABETES IN PATIENTS WITH CHRONIC LIVER DISEASE: FOCUS ON NONALCOHOLIC FATTY LIVER DISEASE.

Raschi E, Mazzotti A, Poluzzi E, De Ponti F, Marchesini G.

Pharmacotherapy used to treat type 2 diabetes mellitus (T2DM) is facing a paradigm shift in clinical practice with recent cardiovascular (CV) outcome trials having a substantial impact on drug prescription with treatment having a more tailored approach. In patients with T2DM, the issue of chronic liver disease is multifaceted. However, a clinical evidence is emerging on the beneficial effect of antidiabetic medications on nonalcoholic fatty liver disease (NAFLD). Areas covered: The authors provide a synopsis on the current and upcoming pharmacotherapy for NAFLD, including the challenges with their development, focusing on drugs for T2DM. Clinical data on the potential benefits and safety issues are assessed with the aim of proposing an individualized algorithm for patient management. Both MEDLINE and ClinicalTrials.Gov are used to derive the relevant information. Expert opinion: Considering the pivotal role of insulin resistance in NAFLD, insulin sensitizers should be the treatment of choice. Accordingly, pioglitazone is the only drug with a significant effect on liver fibrosis, the driver of disease progression and long-term outcome. Among new glucose-lowering drugs, glucagon-like-peptide 1 receptor agonists or sodium-glucose cotransporter type 2 inhibitors have shown positive effects in phase II studies and are qualifying as potential candidates for NAFLD treatment in diabetes.

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Drugs Aging 2018;35(12):1099-1108. doi: 10.1007/s40266-018-0600-0.

ADHERENCE OF ELDERLY PATIENTS WITH CARDIOVASCULAR DISEASE TO STATINS AND THE RISK OF EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: EVIDENCE FROM AN ITALIAN REAL-WORLD INVESTIGATION.

Rea F, Calusi G, Franchi M, Vetrano DL, Roberto G, Bonassi S, Kirchmayer U, Chinellato A, Bettiol A, Sultana J, Mugelli A, Corrao G; I-GrADE Investigators.

Objective: The objective of this study was to investigate the relationship between adherence to statin therapy and the risk of exacerbation among elderly individuals affected by chronic obstructive pulmonary disease and cardiovascular disease.

Methods: Using the healthcare utilisation databases of five Italian territorial units accounting for nearly 35% of the Italian population, we recruited a cohort of 6263 elderly persons (i.e. aged 65 years or older) with co-existing chronic obstructive pulmonary disease and cardiovascular disease who initiated statin therapy. Exposure was adherence to statins measured by the proportion of days of follow-up covered. Outcome was the first hospital admission for chronic obstructive pulmonary disease occurring in the period of observation. A proportional hazards model was used to estimate the hazard ratio and 95% confidence intervals for the exposure-outcome association, after adjusting for several covariates. A set of sensitivity analyses was performed to account for sources of systematic uncertainty.
Results: During an average follow-up of about 4 years, 1307 cohort members experienced the outcome. Compared with patients with low adherence (proportion of days of follow-up covered ≤ 40%), those with intermediate (proportion of days of follow-up covered 41-80%) and high (proportion of days of follow-up covered > 80%) adherence exhibited a lower risk of exacerbation of 16% (95% confidence interval 3-27) and 23% (95% confidence interval 10-34).
Conclusions: In a real-world setting, we observed evidence that adherence to statin therapy markedly reduced the risk of chronic obstructive pulmonary disease exacerbations in elderly patients with co-existing chronic obstructive pulmonary disease and cardiovascular disease. Given the limited and controversial evidence from trials, more randomised controlled trials are urgently needed to better examine the potential benefits of statins as adjunct therapy in chronic obstructive pulmonary disease.

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Patient Prefer Adherence 2018;12:2153-2168. doi: 10.2147/PPA.S168458.

PATIENTS', PHYSICIANS', NURSES', AND PHARMACISTS' PREFERENCES ON THE CHARACTERISTICS OF BIOLOGIC AGENTS USED IN THE TREATMENT OF RHEUMATIC DISEASES.

Scalone L, Sarzi-Puttini P, Sinigaglia L, Montecucco C, Giacomelli R, Lapadula G, Olivieri I, Giardino AM, Cortesi PA, Mantovani LG, Mecchia M.

Objective: To estimate preferences in relevant treatment characteristics evaluated by different groups involved in the management of patients with rheumatic diseases.
Subjects and methods: We surveyed patients with rheumatic diseases, and rheumatologists, nurses, and pharmacists with experience in treatment with/provision of biologic drugs for these patients. Through a discrete choice experiment, participants evaluated 16 possible scenarios in which pairs of similarly efficacious treatments were described with six characteristics: 1) frequency of administration; 2) mode and place of administration; 3) manner, helpfulness, efficiency, and courtesy of health personnel; 4) frequency of reactions at the site of drug administration; 5) severity of generalized undesired/allergic reactions; and 6) additional cost. The direction and strength of

preferences toward each characteristic level and the relative importance of each characteristic were estimated through a random-effects conditional logistic regression model.
Results: In total, 513 patients, 110 rheumatologists, 51 nurses, and 46 pharmacists from 30 centers in Italy participated. Characteristics 3, 4, and 6 were the most important for every subgroup; 1 was least important for patients and rheumatologists, 2 was least important for pharmacists, and 2 and 5 were least important for nurses. For characteristic 2, pharmacists preferred subcutaneous self-injection with a syringe; nurses preferred assisted infusion at an infusion center close to the patient's home; patients and rheumatologists preferred subcutaneous self-injection with a pen.
Conclusions: The different preferences for some characteristics shown by the different groups can play an important role, together with purely clinical aspects, in the choice and consequent benefit of treatments, contributing also to a more satisfactory use of resources.

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BioDrugs 2018;32(6):607-617. doi: 10.1007/s40259-018-0313-2.

Real World Data on the Utilization Pattern and Safety Profile of Infliximab Originator Versus Biosimilars in Italy: A Multiregional Study.

Scavone C, Sessa M, Clementi E, Corrao G, Leone R, Mugelli A, Rossi F, Spina E, Capuano A.

Background: In recent years, several biosimilar drugs, including those of infliximab, have obtained marketing authorization from the European Medicines Agency (EMA). Given the peculiarity of the safety profile of biological medical products (originator and biosimilars), the evaluation of their tolerability represents an important component of pre-marketing and post-marketing clinical development. For example, infliximab products may cause adverse drug reactions (ADRs) including acute infusion reactions, delayed hypersensitivity reactions, and loss of efficacy, as a direct consequence of immunogenicity. Therefore, specific contraindications, special warnings and precautions have been introduced in the infliximab Summary of Product Characteristics (SPC).
Objective: The aim was to assess the magnitude of preventable ADRs in individual case safety reports (ICSRs) having infliximab as a suspected drug across Italy (using the spontaneous reporting systems), and the probability of reporting infections, infusion reactions, lack of efficacy, and hypersensitivity for originator and biosimilars of infliximab.
Methods: We analyzed ADRs reported across the 2015-2017 period in the databases of five Italian regions: Campania, Lombardy, Sicily, Tuscany, and Veneto. Preventability of ADRs was assessed using the P-method. To compare the probability of reporting infections, infusion reactions, lack of efficacy, and hypersensitivity as ADRs as opposed

to other types of ADRs between originator and biosimilars of infliximab, we used the reporting odds ratio (ROR). For descriptive purposes, the number of ICSRs involving infliximab, the number of infliximab vials distributed in the aforementioned Italian regions and the relative reporting rate stratified by semester were reported.
Results: From October 2015 to October 2017, 459 ICSRs reported infliximab as a suspected drug (222 ICSRs related to infliximab originator and 237 to infliximab biosimilars). In the same period, 81,906 vials of infliximab were distributed, resulting in a reporting rate of six ICSRs/1000 vials. Overall, 34 cases (7.41%) were categorized as preventable. The most frequently detected critical criteria were "documented hypersensitivity to administered drug or drug class," "inappropriate prescription for patient's underlying medical condition" and "incorrect dose." Biosimilars had, in adjusted analyses, an increased probability of being reported as suspected in ICSRs reporting infusion reactions (ROR 4.09; 95% confidence interval [CI] 1.26-13.32) when compared to Remicade®. On the contrary, they had a decreased probability of being reported as suspected in ICSRs reporting infections or lack of efficacy (ROR 0.33; 95% CI 0.12-0.89; ROR 0.35; 95% CI 0.20-0.61).
Conclusions: Our study demonstrates that, along with a rapid increase in the utilization of infliximab biosimilars across Italy, there was also an increase in reporting ADRs induced by infliximab biosimilars. Of the reported ADRs, 7.4% were considered preventable. In adjusted analyses, infliximab biosimilars were shown to have an increased probability of being reported as suspected drugs in infusion reactions and a decreased probability of being reported as suspected drugs in cases of lack of efficacy or infection. Considering the potential advantages offered by the utilization of biosimilars in clinical practice, we believe that the use of biosimilars, including those of infliximab, should be supported. In order to achieve this aim, increased knowledge on safety and efficacy of biosimilar drugs should be obtained from real world clinical practice.

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J Clin Gastroenterol 2019;53(1):15-22. doi: 10.1097/MCG.0000000000000962.

Diagnostic Yield of 2 Strategies for Adult Celiac Disease Identification in Primary Care.

Scoglio R, Trifirò G, Sandullo A, Marangio G, D'Agate C, Costa S, Pellegrino S, Alibrandi A, Aiello A, Currò G, Cuzzupè C, Comisi F, Amato S, Conti Nibali R, Oteri S, Magazzu G, Carroccio A; Sicilian Celiac Disease Study Group.

Goals: To compare the diagnostic yield and cost-consequences of 2 strategies, screening regardless of symptoms versus case finding (CF), using a point-of-care test (POCT), for the detection of celiac disease (CD) in primary care, to bridge the diagnostic gap of CD in adults.

Materials and methods: All subjects under 75 years of age who consecutively went to their general practitioners' offices were offered POCT for anti-transglutaminase immunoglobulin A antibodies. The POCT was performed on all subjects who agreed, and then a systematic search for symptoms or conditions associated with higher risk for CD was performed, immediately after the test but before knowing the test results. The 2 resulting groups were: (a) POCT positive and (b) symptomatic subject at CF. Subjects were defined as symptomatic at CF in the presence of 1 or more symptoms. All POCT-positive or symptomatic subjects at CF were referred to the CD Centers for confirmation of CD. Data on resource consumption were gathered from patients' charts. Cost of examinations, and diagnostic and laboratory tests were estimated with regional outpatient tariffs (Sicily), and a price of &OV0556;2.5 was used for each POCT.
Results: Of a total of 2197 subjects who agreed to participate in the study, 36 (1.6%) and 671 (30.5%) were POCT positive and symptomatic at CF, respectively. The yield from the screening and CF was 5 new celiac patients. The total cost and mean cost for each new CD case were &OV0556;7497.35 and &OV0556;1499.47 for the POCT screening strategy, and &OV0556;9855.14 and &OV0556;1971.03 for the CF strategy, respectively. Assuming consecutive use of both strategies, performing POCT only in symptomatic subjects at CF, the calculated yield would be 4 new diagnoses with a total cost of &OV0556;2345.84 and a mean cost of &OV0556;586.46 for each newly diagnosed patient. Only 1 patient was celiac despite a negative POCT.
Conclusions: Testing symptomatic subjects at CF only by POCT seems the most cost-effective strategy to bridge the diagnostic gap of adult CD in primary care.

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BioDrugs 2018;32(4):367-375. doi: 10.1007/s40259-018-0293-2.

Comparative Safety of Originator and Biosimilar Epoetin Alfa Drugs: An Observational Prospective Multicenter Study.

Stoppa G, D'Amore C, Conforti A, Traversa G, Venegoni M, Taglialatela M, Leone R; ESAVIEW Study Group.

Background: Erythropoiesis-stimulating agents (ESAs) are biological molecules approved for the treatment of anemia associated with chronic renal failure. Biosimilars were licensed for use in Europe in 2007.
Aim: This study aimed to compare the safety profile of biosimilars with respect to the reference product in a nephrology setting.
Methods: A prospective study was conducted in four Italian regions between 1 October 2013 and 30 June 2015. The study population included patients aged ≥ 18 years undergoing hemodialysis and treated with epoetins as per the clinical practice of the participating centers. The two comparison cohorts included patients treated with either an originator or a biosimilar epoetin alfa. Each patient was followed up until occurrence

of any safety outcome of interest (grouped into three major categories), switch to a different ESA product, transplant or peritoneal dialysis, death, or end of the study period, whichever came first.
Results: Overall, 867 subjects were included in the study (originator: N = 423; biosimilar: N = 444). Biosimilar users were older than originator users (median age of 76 vs 64 years, respectively), more frequently affected by arrhythmia (29.3 vs 22.5%), and less frequently candidates for transplantation (3.8 vs 18.2%). Cox-regression analysis showed no increase in risk of safety outcomes in biosimilar users, even after adjusting for confounding factors: 1.0 (95% confidence interval [CI] 0.7-1.3) for any outcomes; 1.1 (95% CI 0.7-1.8) for problems related to dialysis device; 0.9 (95% CI 0.6-1.5) for cardio- and cerebro-vascular conditions; 0.9 (95% CI 0.6-1.5) for infections.
Conclusions: This study confirms the comparable safety profiles of originator and biosimilar epoetin alfa drugs when used in patients receiving dialysis.

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Expert Opin Drug Metab Toxicol 2019;15(2):179-188. doi: 10.1080/17425255.2019.1561860.
ALL-CAUSE MORTALITY AND ANTIPSYCHOTIC USE AMONG ELDERLY PERSONS WITH HIGH BASELINE CARDIOVASCULAR AND CEREBROVASCULAR RISK: A MULTI-CENTER RETROSPECTIVE COHORT STUDY IN ITALY.
Sultana J, Giorgianni F, Rea F, Lucenteforte E, Lombardi N, Mugelli A, Vannacci A, Liperoti R, Kirchmayer U, Vitale C, Chinellato A, Roberto G, Corrao G, Trifirò G.
Background: Little is known about the comparative risk of death with atypical or conventional antipsychotics (Aps) among persons with cardiovascular or cerebrovascular disease (CCD).
Research design and methods: A cohort study was conducted using five Italian claims databases. New atypical AP users with CCD aged ≥65 (reference) were matched to new conventional AP users. Mortality per 100 person years (PYs) and hazard ratios (HR), estimated using Cox models, were reported. Incidence and risk of death were estimated for persons having drug-drug interactions. Outcome occurrence was evaluated 180 days after AP initiation.
Results: Overall 24,711 and 27,051 elderly new conventional and atypical AP users were identified. The mortality rate was 51.3 and 38.5 deaths per 100 PYs for conventional and atypical AP users. Mortality risk was 1.33 (95%CI: 1.27-1.39) for conventional APs. There was no increased mortality risk with single drug-drug interactions (DDIs) vs. no DDI. AP users with ≥ 1 DDI had a 29% higher mortality risk compared to no DDI in the first 90 days of treatment (HR: 1.29 (95% CI: 1.00 - 1.67)).
Conclusions: Conventional APs had a higher risk of death than atypical APs among elderly persons with CCD. Having ≥1 DDI was associated with an increased risk of death.

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Drug Saf 2019 Jan 8. doi: 10.1007/s40264-018-00785-z.

Identifying Data Elements to Measure Frailty in a Dutch Nationwide Electronic Medical Record Database for Use in Postmarketing Safety Evaluation: An Exploratory Study.

Sultana J, Leal I, de Wilde M, de Ridder M, van der Lei J, Sturkenboom M, Trifirò G.

Introduction: The role of frailty in postmarketing drug safety is increasingly acknowledged. Few European electronic medical records (EMRs) have been used to explore frailty in observational drug safety research.

Objective: The aim of this study was to identify data elements, beyond multimorbidity and polypharmacy, that could potentially contribute to measuring frailty among older adults in the Dutch nationwide Integrated Primary Care Information (IPCI) database.

Methods: Persons aged between 65 and 90 years in the IPCI database were identified from 2008 to 2013. Clinical non-disease, non-drug measurements that could potentially contribute to measuring frailty were identified and selected if they were recorded in > 0.005% of patients and could be included in at least one of three definitions of frailty: the frailty phenotype model, the cumulative deficit model, and direct evaluations of frailty through standardized frailty scores. The frequency of these measures was calculated.

Results: Overall, 314,191 (17% of the source population) elderly persons were identified. Of these, 7948 (2.53%) had one or more of 12 clinical measurements identified that could potentially contribute to measuring frailty, such as clinical evaluations of cognition, mobility, and cachexia, as well as direct measures of frailty, such as the Groningen Frailty Index. Three of five measurements required for the frailty phenotype were identified in < 0.5% of the population: cachexia, reduced walking speed, and reduced physical activity; weakness and fatigue were not identified. The measurements outlined above may be appropriate for the cumulative deficit definition of frailty, provided that at least 30 deficits, including comorbidities and drug utilization, are evaluated in total. The most commonly recorded item identified that could potentially be used in a cumulative frailty model was the Mini-Mental State Examination score (N= 2850; 0.91%); the only recorded direct measurement of frailty was the Groningen Frailty Index (N = 2382; 0.76%).

Conclusions: Non-disease, non-drug clinical data that could potentially contribute to a frailty model was not commonly recorded in the IPCI; less than 3% of a cohort of elderly persons had these data recorded, suggesting that the use of these data in postmarketing drug safety evaluation may be limited.

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Drug Saf 2018 Dec 18. doi: 10.1007/s40264-018-0768-6.

WORKSHOP ON THE ITALIAN PHARMACOVIGILANCE SYSTEM IN THE INTERNATIONAL CONTEXT: CRITICAL ISSUES AND PERSPECTIVES.

Sultana J, Moretti U, Addis A, Caduff P, Capuano A, Kant A, Laporte JR, Lindquist M, Raine J, Sartori D, Trifirò G, Tuccori M, Venegoni M, van Puijenbroek E, Leone R.

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Drug Saf 2018;41(11):1003-1011. doi: 10.1007/s40264-018-0681-z.

WHAT FUTURE HEALTHCARE PROFESSIONALS NEED TO KNOW ABOUT PHARMACOVIGILANCE: INTRODUCTION OF THE WHO PV CORE CURRICULUM FOR UNIVERSITY TEACHING WITH FOCUS ON CLINICAL ASPECTS.

van Eekeren R, Rolfes L, Koster AS, Magro L, Parthasarathi G, Al Ramimmy H, Schutte T, Tanaka D, van Puijenbroek E, Härmark L.

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

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Eur J Nucl Med Mol Imaging 2018 Dec 7. doi: 10.1007/s00259-018-4230-x.

MONITORING RESPONSE OF ADVANCED MERKEL CELL CARCINOMA TO AVELUMAB WITH 18F-FDG PET/CT.

Vellani C, D'Ambrosio D, Licata L, Vacchieri I, Bernardo A, Trifirò G.


Convegno AIE Primavera 2019
Epidemiologia e letteratura: un viaggio nella biblioteca del tempo
Il convegno è dedicato alla diffusione scientifica attraverso una "passeggiata" nella letteratura epidemiologica tra passato, presente e futuro. Durante questo percorso ci accompagneranno coloro che hanno contribuito, contribuiscono e contribuiranno all'epidemiologia italiana. Le conoscenze scientifiche crescono e cambiano rapidamente e spesso tenere il passo con i nuovi metodi è faticoso. Una visione chiara del passato può però essere utile per affrontare le nuove sfide odierne, soprattutto quando le "vecchie" sfide sembrano essere ancora attuali. Il convegno ha lo scopo di collegare le diverse sfumature dell'epidemiologia tramite il massimo comun divisore: la letteratura scientifica.
18-19 | 3 | 2019
Regione Emilia Romagna, Terza Torre
Viale della fiera, 8 - Bologna
Giorno 1 18 | 03 | 2019
mattina
10.00 - Workshops tematici
• Scrivere un articolo per E&P e non solo
• Etica della pubblicazione scientifica
• I molti volti della Farmacoepidemiologia
• Metodi avanzati per la sintesi delle informazioni

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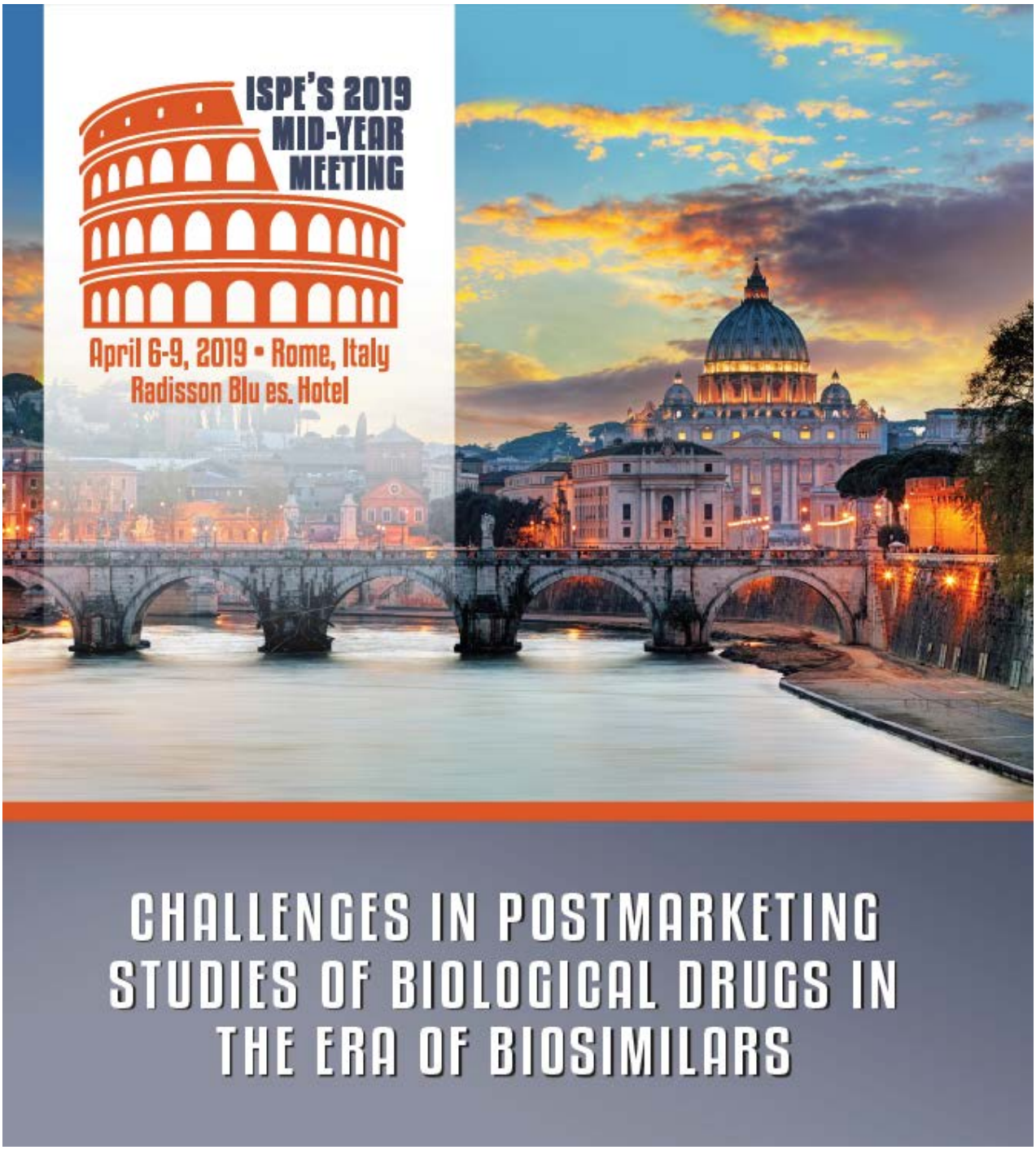
6-9	**CHALLENGES IN POSTMARKETING STUDIES OF**
APR	**BIOLOGICAL DRUGS IN THE ERA OF BIOSIMILAR**
2019	*Radisson Blu Hotel - Roma*

https://www.pharmacoepi.org/meetings/mid-year-2019/agenda/



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Philadelphia Convention Center – Philadelphia, PA (USA)

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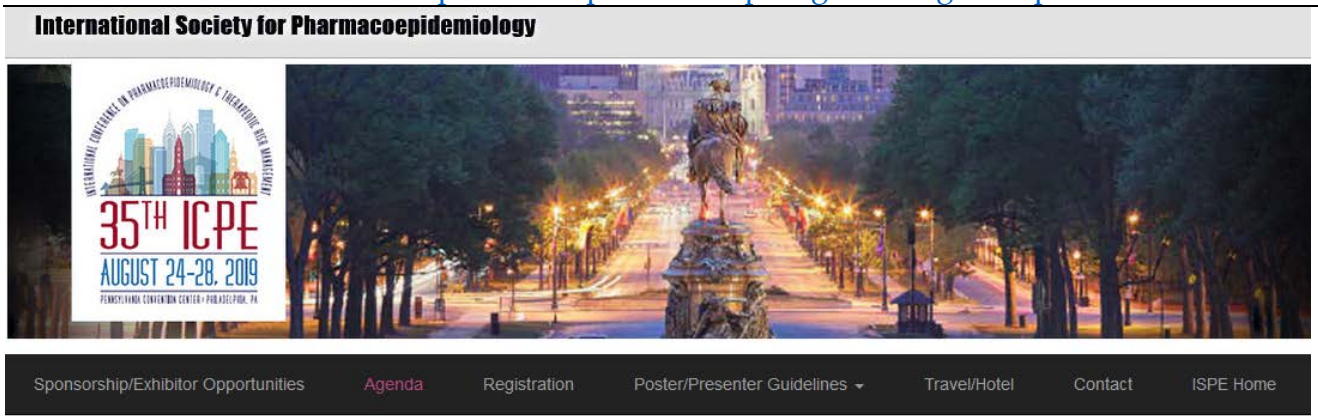

INFORMAZIONI GENERALI

DATE DEL CONGRESSO
20-23 Novembre 2019

SEDE CONGRESSUALE
Palazzo dei Congressi di Firenze
Piazza Adua, 1
50121 - Firenze

Ulteriori segnalazioni …

Proseguono i Journal Club di Farmacoepidemiologia organizzati dall'ARS Toscana.
Per il calendario degli appuntamenti e ulteriori informazioni:

https://www.ars.toscana.it/temi/journalclub_farmacoepidemiologia/

Prossimo evento:
8 febbraio 2019
14:15-16:15

TEMA della giornata "**Real-world evidence & Risk minimization**".

Janet Sultana, del Dipartimento di scienze biomediche, odontoiatriche e delle immagini morfologiche e funzionali dell'Università di Messina, presenterà "**Role of real-world evidence in measuring the impact of risk minimisation**".

È in uscita (entro la fine di febbraio) il bollettino dell'EuroDURG
che sarà scaricabile al sito:

https://www.pharmacoepi.org/eurodurg/

e inoltre … prossime scadenze:

- ✓ **invio abstract congresso ispe: 13 febbraio 2019**
- ✓ **invio abstract congresso eacpt: 14 febbraio 2019**