Abstracts of the XXX Annual Meeting of the Spanish Society of Clinical Pharmacology, 3rd–5th October 2018, Santander, Spain
Aims and Scope

Basic & Clinical Pharmacology & Toxicology is an independent journal, publishing original scientific research in all fields of toxicology, basic and clinical pharmacology. This includes experimental animal pharmacology and toxicology and molecular (-genetic), biochemical and cellular pharmacology and toxicology. It also includes all aspects of clinical pharmacology: pharmacokinetics, pharmacodynamics, therapeutic drug monitoring, drug/drug interactions, pharmacogenetics/-genomics, pharmacoepidemiology, pharmacoepidemiology, pharmacoepidemiology, randomized controlled clinical trials and rational pharmacotherapy. For all compounds used in the studies, the chemical constitution and composition should be known, also for natural compounds.

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CONFERENCE PROGRAM

XXX SEFC CONGRESS

Wednesday 3 October 2018
Magdalena Palace

19:30–20:15
INAUGURAL CONFERENCE
“How to reconcile the therapeutic needs of the population with the personalized medicine challenge”
Emilio Vargas Castrillón MD, PhD. Head of the Clinical Pharmacology Service, Hospital Clínico San Carlos. Madrid. Professor of Pharmacology, Universidad Complutense de Madrid.

Thursday 4 October 2018
Valdecilla Auditorium “Dr Carlos Gómez-Durán”

08:15–09:15
PLENARY LECTURE
“How can we trust claims from clinical trial reports?”
Prof. Stuart J. Pocock, Department of Medical Statistics, London School of Hygiene and Tropical Medicine. London

09:30–11:30
TABLE 1: CLINICAL PHARMACOLOGY WITHIN PERSONALISED MEDICINE CONTEXT

Moderators: Consuelo Rodríguez MD, PhD. Clinical Pharmacology Service, Hospital Universitario de Canarias. Santa Cruz de Tenerife
Antonio Carcas, MD, PhD. Associate Professor, Universidad Autónoma de Madrid, Clinical Pharmacology Service, Hospital Universitario La Paz, IdiPAZ, Madrid

09:30–09:50
“Precision Medicine: pharmacogenetic and pharmacodynamic implications”
Francisco Abad Santos MD, PhD. Clinical Pharmacology Service, Clinical Trial Unit Director, Hospital Universitario La Princesa. Madrid

09:50–10:10
“The correct drug at the correct dose: The role of pharmacokinetic and therapeutic drug monitoring (TDM) in personalised medicine”
Mar García Sáiz MD, PhD. Head of the Clinical Pharmacology Service, Hospital Universitario de Canarias. Santa Cruz de Tenerife

10:10–10:30
“Patient oriented research: Do we need new methodological approaches?”
José Antonio Sacristán MD, PhD. Medical Director, Lilly Spain. Madrid

10:30–10:50
“Humanizing healthcare: the other side of the coin of personalized medicine”
Pilar Bravo Agüí RN. Nurse and Bioethics Master Degree. Hospital Universitario Puerta de Hierro, Majadahonda Madrid

10:50–11:30
Q&A

12:00–13:30
Oral Presentations

Moderators: Belén Ruiz Antorán, MD, PhD. Clinical Pharmacology Service, Hospital Universitario Puerta de Hierro Majadahonda. Madrid
Gina Paola Mejía MD, Clinical Pharmacist, Hospital Universitario de La Princesa. Madrid

13:30–14:00
Posters Presentation

15:00–15:30
Posters Presentation

15:30–17:00
TABLE 2: THE IMMUNE SYSTEM AND ITS PLACE IN THERAPY

Moderators: Arancha Sancho López MD. Clinical Pharmacologist, IIS Puerta de Hierro-Segovia de Arana. Majadahonda
Mónica Saldaña Valdés MD. Clinical Pharmacologist, Hospital Universitario Puerta del Mar. Cádiz

15:30–16:00
“The immune system and cancer”
Almudena García Castaño MD, PhD. Medical Oncology Service. Hospital Universitario Marqués de Valdecilla. Santander
16:00–16:30  “CART cells in leukaemia and other hematologic malignancies”
Julio Delgado González MD, PhD. *Haematologist. Hospital Clinic. Barcelona*

16:30–17:00  Q&A

17:00–17:30  Posters Presentation

17:30–19:30  SEFC Assembly

**Friday 5 October 2018**  
**Valdecilla Auditorium**“Dr Carlos Gómez-Durán”

08:55–09:55  Oral Presentations
Moderators: Judith Sanabria Cabrera MD. *Clinical Pharmacologist, IBIMA, Hospital Universitario Virgen de la Victoria. Málaga*

Pedro Zapater Hernández, MD, PhD. *Clinical Pharmacology Service, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Alicante*

09:55–12:30  **TABLE 3: CONTRIBUTION OF THE CLINICAL PHARMACOLOGY TO THE QUALITY OF DRUG PRESCRIPTION**
Moderators: Cristina Avendaño Solá MD, PhD. *President of the Spanish Clinical Pharmacology Society*

Ana Tejerina Puente MD, *Deputy Director of Health Assistance of the Cantabrian Health Service*

10:00–10:30  “Teaching of clinical pharmacology and therapeutics in faculties of medicine”
Dolors Capellá Hereu MD, PhD. *Professor of Clinical Pharmacology. Universidad de Girona*

10:30–11:00  “Clinical Pharmacology in continuing medical education”
Antònia Agustí Escasany MD, PhD. *Clinical Pharmacology Service, Hospital Universitari Vall d’Hebron. Barcelona*

11:30–12:00  “Clinical Pharmacology in Primary Healthcare”
Rosa Morros Pedrós. MD, PhD. *Clinical Pharmacologist IDIAP Jordi Gol. Barcelona*

12:00–12:30  Q&A

12:30–13:15  **CLOSING SEMINAR**
“New Challenges in Drug Evaluation and Drug Selection”
Caridad Pontes García MD, PhD. *Gerent d’Harmonització Farmacoterapèutica. Servei Català de la Salut. Barcelona*

13:15–13:45  Awards Ceremony

14:00  CLOSURE
Cantabria Minister of Health, President of Cantabria Medical Council, Managing Director of Cantabrian Health Service, Managing Director of University Hospital “Marqués de Valdecilla”, SEFC President and Congress Organizing Committee President

15:30–17:00  Therapeutic Drug Monitoring Workshop
INAUGURAL CONFERENCE

001  | How to reconcile the therapeutic needs of the population with the personalized medicine challenge

Emilio Vargas Castrillón\textsuperscript{1,2}; Marta Pavía Hernández\textsuperscript{3}

\textsuperscript{1}Department of Clinical Pharmacology – Hospital Clínico San Carlos, Madrid, Spain; \textsuperscript{2}Pharmacology -, Universidad Complutense de Madrid, Spain; \textsuperscript{3}Research Institute of the Hospital Clínico San Carlos – Hospital Clínico San Carlos, Madrid, Spain

The concept individualized or personalized medicine raised its usage in the past decades. The traditional approach to pharmacotherapy understood as the uniformly use of drugs in a patient population seems to isolate a concept that always existed: personalized medicines, because medicine has always considered the needs of an individual.

During the past years, the transition of the concept has been motivated by the inclusion of new fields in the therapeutic decision: pharmacogenetics, pharmacogenomics and biomarkers. Although it doesn’t exist a universally accepted definition, the EU Health Ministers in their Council conclusions on personalised medicine for patients defined it as “Personalised medicine refers to a medical model using characterisation of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.”

This presentation aims to cover the discussion of how the needs of society can be impacted by this new paradigm, including the potential for uneven access to health and the sustainability of the National Health Service. Moreover, the challenges from the public funder perspective, make available this personalized medicines in a cost-effective way.

The possibility to identify risks for disabling health problems, choosing the treatment strategy most likely to benefit specific patient groups, and mitigating risk is a vital strategy in the effort to provide better health care. However, it should as well include the possibility to decrease the needs of healthcare resources (avoiding days of hospitalization, surgical interventions, and other procedures) and provide stability to pharmaceutical expenditure, allowing the system sustainability.

However, this statement can only be true if the potential increase in safety and efficacy is demonstrated through reliable and good quality evidence (within well-designed clinical trials), and the effectiveness in a significant gain of quality-adjusted life years.

During the last 10 years, the number of drugs including pharmacogenetic biomarkers authorised by the European Medicine Agency (EMA) has increase in approximately 20\%, but this new drugs marketed are generally increasing prices, and this incremental cost in several cases has not a direct relation with the innovation value. Furthermore, this substantial increase of the cost, is not just related to the drug, but to further procedures associated to the use of the medication (for example molecular analysis).

The challenges in the management incorporation in our Health System of these new drugs affect the micro, meso and macro levels.

Macro-management: Although the Health Ministry has already expressed the importance of continuing advancing in the incorporation of Personalized Medicine in our health system, two actions should be studied in the short-term: (a) The definition of a National Strategy in the implementation of Personalized Medicine, as the one already developed in France. (b) The creation of reimbursement policies for the new diagnostic tests or procedures based on biomarkers.

On the other hand, the increase of the budget pressures has resulted in a bigger role for regions in price negotiation and risk sharing between the Spanish authorities and pharmaceutical companies.

Meso-management: At this level, new strategies should be developed to optimize the access of an affordable personalized medicine. One of the options, already implemented in some hospitals, can be the payment due to results: a risk sharing option that will require a strong method to capture data on outcomes. As well, the implementation of training programs to capacitate the physicians in the new treatment management, diagnose and follow up procedures. Furthermore, the creation and development of pharmacogenetics, and pharmacogenomics units on the hospitals will conduct to the success implementation of the personalized medicine.
Micro-Management: At this level, the activities will be fundamentally oriented to a pragmatic cost restriction, through the prescription recommendation and indicators.

The generalization of the use of personalized medicine could increase the therapeutic success and the quality of our National Health Service, although it would probably increase cost. That is why the prioritization and cost-economic evaluation of these interventions must be carefully considered before making decisions and a proactive management at all the sanitary levels should be implemented.

PLENARY LECTURE

002  |  Can we trust claims from clinical trial reports?
Stuart J. Pocock
Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, England

The aim of this talk is to outline some key issues to consider when undertaking constructive critical appraisal of a clinical trial report. Recent major trial publications, mainly in cardiovascular diseases, will illustrate each point.

Issues to consider include: bias in trial design (e.g. lack of blinding), the abuse of P-values, the need to document statistical uncertainty, estimation of absolute benefit (e.g. no. needed to treat), assessing the totality of evidence (e.g. primary and secondary endpoints), interpretation of composite endpoints, caution re trials that stop early, multiplicity of data (e.g. subgroup analyses, and claims based on “positive spin”), the bias of incomplete follow-up, analysis by intention to treat, the trade-off between efficacy and safety, and assessing individual patient risk in determining which treatment is best for the next patient.

For those wishing to read more the author has a series of relevant articles in J AmerColl Cardiology, four in Dec 2015 and one in June 2018.

003  |  Precision medicine: Pharmacogenetic and pharmacodynamic implications
Francisco Abad Santos
Clinical Pharmacology Service, Clinical Trial Unit Director, University Hospital “La Princesa”, Madrid, Spain

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. This approach will allow doctors to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Precision medicine often involves the application of genomic analysis and systems biology to analyze the cause of an individual patient’s disease at the molecular level and then to utilize targeted treatments (possibly in combination) to address that individual patient’s disease process. The patient’s response is then tracked as closely as possible, often using surrogate measures (pharmacodynamics), and the treatment finely adapted to the patient’s response.

There is a lot of overlap between the terms “precision medicine” and “personalized medicine,” but the first is preferred because the word “personalized” could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual.

As a fundamental element in precision medicine, pharmacogenomics, the study of responses of individuals to medication based on their genomic information, enables the evaluation of some specific genetic variants responsible for an individual’s particular drug response. It combines pharmacology and genomics to develop effective, safe medications and doses that are tailored to variations in a person’s genes.

Artificial intelligence is essential for the advancement of precision medicine. Machine learning algorithms are used for genomic sequence and to analyze and draw inferences from the vast amounts of data patients and healthcare institutions recorded in every moment (Big Data). Artificial intelligence techniques can be used in precision medicine
to understand genotypes and phenotypes in existing diseases, improve the quality of patient care, enable cost-effectiveness, and reduce readmission and mortality rates.

Physiologically based pharmacokinetics (PBPK) models are relatively new in drug development and healthcare. However it can be viewed as a natural extension of traditional empirical compartmental and noncompartmental pharmacokinetic/pharmacodynamic (PK/PD) modeling techniques with increased model complexity and greater fidelity to underlying physiological mechanisms and phenomena.

Population based PBPK models have a unique advantage by considering not only the drug and the formulation characteristics but also the underlying physiology of the individual subject and its variability within a population in prediction of drug absorption, distribution and elimination. PBPK models have already been used to predict drug-drug interactions and oral drug absorption. Other advantage of PBPK approach is the possibility of extrapolations. Once the model performance is verified for a particular drug/formulation in one population, it can be assessed with increased confidence for another population. This makes possible to transfer the physiological information from healthy volunteers to elderly patients, provided the physiological differences between healthy and elderly populations are well characterized. The same concept is potentially applicable to personalized medicine in that a validated population PBPK model can be used to individualize dosing by combining individual physiological information with mathematical optimization techniques. However, personalized medicine with PBPK modeling still has a long way to go.

004 | The correct drug at the correct dose: The role of pharmacokinetic and Therapeutic Drug Monitoring (TDM) in personalised medicine

Mª del Mar García Sáiz
Clinical Pharmacology Service, Canarias University Hospital, Santa Cruz de Tenerife, Spain

Traditionally, TDM involves measuring drug concentrations in biological fluids and interpreting these concentrations in terms of clinical parameters. The aim of TDM is to optimize pharmacotherapy by maximizing therapeutic efficacy, while minimizing adverse-events, because the blood-concentration of the drug is a better predictor of the desired effects than the dose. In addition, TDM can also be useful in cases of non-compliance, where dosage adjustment is required as a result of drug-interactions, and where intoxication is suspected.

TDM is clinically relevant and cost-effective when the clinician orders the monitoring with an appropriate indication, the blood sample is drawn at the correct time, the analysis is performed using a method with appropriate accuracy and precision, and the results are interpreted and used correctly through the application of pharmacokinetic principles and clinical criteria. These interpretations and individualized dosing recommendations should be provided by adequately trained health care professionals (e.g. clinical pharmacologists).

A systematic review carried out in 2005, documented the information on the rationale and cost-effectiveness of TDM for different drug classes. The importance and cost-effectiveness of TDM is well described for aminoglycosides, and for vancomycin in selected patient populations (oncology or intensive-care-unit patients and patients with nephrotoxic drugs). TDM of the classic antiepileptic-drugs can be cost-effective and can lead to better control of patients with few side-effects; however, TDM of the modern antiepileptic-drugs appears to be useful in titrating patients with uncontrolled epilepsy and in cases of non-compliance or drug-interactions. For therapy with digoxin, TDM may be useful to guide therapy in cardiac failure and in patients with rapid atrial fibrillation. Therapy with immunosuppressants must be guided by TDM because of wide interindividual variability and risks for drug interactions, but also because of costs associated with transplant-rejection. Respect to psychiatric-drugs, therapy with lithium, tricyclic-antidepressants, haloperidol, and clozapine should be guided with TDM. For the HIV-drugs, TDM of nelfinavir is clearly useful. Although there are no studies that investigate the cost-effectiveness of TDM for many of these drug groups, TDM is considered as standard of care, and many of these drugs could not be used as effectively due to risks of either underdosing or serious toxicity.

In the last years, new areas for TDM have been developed. For instance, the TDM of biologic-agents, mainly anti-TNF drugs, is increasingly used to manage inflammatory-bowel diseases and rheumatoid arthritis, but the cost-effectiveness of this strategy is still debated. There has been also an increase in research related to TDM of other antimicrobial agents, particularly β-lactams, due to concerns about underdosing in critically-ill patients. Moreover, the importance of antifungal TDM is increasingly recognized in clinical practice and TDM is generally indicated for triazoles (itraconazole, voriconazole and posaconazole) and 5-fluorocytosine. In the cardiovascular area, the British Society of Haematology has stated that measuring the plasma drug concentration of direct-oral-anticoagulants, by non-coagulation tests, may be required for optimal drug dosage in patients with impaired renal function, subjected to drug-interactions, or at extremes of body-weight.

New technologies for drug analysis, chromatographic and immunochemistry methods, have been fundamental in the establishment of TDM in routine practice over the years, and
improvements of analytical methods should be continuously performed. The more recent development in liquid-chromatography combined with mass-spectrometry (LC-MS), has resulted in a new potential tool for future TDM service.

Another interesting promise tool is the use of novel biological matrices for TDM. Two such possibilities are dried-blood-spots (DBS) and oral fluid. The potential of DBS is its ability to simplify blood collection.

In conclusion, nowadays, TDM represents an early approach to personalised medicine. Pharmacokinetic-monitoring combined with pharmacogenetic information and measurement of biomarkers (pharmacodynamic-monitoring) is the way to optimize the pharmacotherapy of individual patients.

005 Patient oriented research: Do we need new methodological approaches?
José Antonio Sacristán
Lilly, Spain

The randomized controlled trial (RCT) has become the cornerstone for evaluating treatments’ effectiveness, and the pillar supporting Evidence-Based Medicine (EBM). Their results show whether, in the average patient, one intervention is better than the alternative option. The language of populations is the prevailing language of the EBM movement, based on the evaluation of interventions, the analyses of aggregated data and large sample sizes, the predominance of quantitative methods, the results for the average patients, and the perspective of the regulators.

By speaking the language of populations, EBM has moved away from individual patients. Patient centered medicine (PCM) is developing alongside the concept of personalized medicine and tailored therapeutics. PCM has been defined as the medical practice aimed at improving the health outcomes of individual patients in everyday clinical practice, taking into account their preferences, objectives and values, as well as the available economic resources. Patient-centered medicine should focus on the language of individuals, the evaluation of patients, subgroups analyses, the use of qualitative methods, and the use of outcomes relevant for patients, taking into account their preferences, goals, and values.

As the best decision for the average patient is not necessarily the best decision for the individual patient, PCM needs the development of patient oriented research.

Patient-oriented research requires analyzing the heterogeneity of different types of patients, moving from the study of interventions to the study of patients, the mechanisms of diseases and the identification of the genotypic and/or phenotypic factors that determine different types of patients with different prognoses and responses. Patient-oriented research will also require moving from inductive reasoning, which tries to generalize from an accumulation of cases, towards a hypothetical-deductive logic, based on confronting the theory with the individual facts. The “truth” created by the aggregation of cases should be considered provisional, while observations provide the definitive evidence for the individual patient. A true patient oriented research should also put its focus on patients’ goals, preferences and values. More n-of-1 trials should be conducted, as they are the purest form of tailored clinical research and have been placed by some authors in the first place in the hierarchy of evidence. These studies are the formalization of the “trial of therapy” that the physician conducts in his regular practice, with the enormous advantage that patients benefit directly from research results.

Clinical observations should recover a predominant position in patient-oriented research. Individual cases and case series have been considered the lowest level of evidence but are often the “first line of evidence.” Sometimes a series of cases on a serious adverse effect is sufficient to alter the risk-benefit profile of a drug. In the same way, the observation of “unexpected” cases that do not respond or respond differently to treatment could be of great value in clinical research.

Moving towards tailored clinical research entails specifically allotting more weight to the “medical” component within the research process, by integrating research and clinical practice and accepting that each medical act has the structure of an experiment. Systematization of the observations and experiences of physicians would be of great interest in the analysis of the characteristics and variations in patients’ responses. The development of learning health care systems are becoming a reality thanks to the development of electronic health records and the increasing use of big data. The development of information-based technologies can help to close the gap between physicians and researchers, between patients enrolled in clinical trials and real life patients, and between the clinical report form and the clinical record.

006 Humanizing healthcare: The other side of the coin of personalized medicine
Pilar Bravo Agüí
Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain

Scientific advances in biotechnology and medicine, including targeted therapy in pharmacology and sequencing technologies, have allowed increasing personalized clinical management. In addition to these technical aspects, personalization of healthcare also implies respecting patient
values, taking their preferences and needs into account and adequately managing communication, information and patient education as well as providing emotional support and involving the patient’s family throughout the healthcare process. Personalizing healthcare through humanization can significantly impact patient-perceived and professional-provided quality care, respectively, and is an additional element of quality care and personalized medicine.

From the Hippocratic Code to Confucius and other philosophers throughout history, medicine has been considered a discipline with the moral compromise of mitigating patient suffering. This humanizing perspective of medicine must not only be aimed towards the patient but also towards other professionals and administrators. It is not possible to develop such a mission if those who must take it into action are not treated with the same principles they promote.

Healthcare professions are intrinsically human as they are focused towards the promotion of health, minimization of suffering and the connection with human vulnerability. Beyond technical and scientific abilities and knowledge, the development of healthcare professions must consider patients as human beings in all their dimensions. The consideration of others in a personalized manner will lead us towards a humanized healthcare.

There are many healthcare institutions that openly declare humanizing healthcare principles and develop institutional policies centered towards promoting excellence through humanization. Such policies have been included as part of the health policies of some Autonomous Communities.

| TABLE 2 THE IMMUNE SYSTEM AND ITS PLACE IN THERAPY |

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007  | The immune system and cancer

Almudena García Castaño
Servicio Oncología Médica, HU Marqués de Valdecilla, Santander, Spain

The relationship between the immune system and cancer is extraordinarily complex. The cells of the tumor although they are very similar to the normal ones display some different characteristic reason why they are recognized by the immune system that naturally tends to destroy them. In fact, the theory of immunological surveillance makes us understand why cancer is more frequent in patients with immunodeficiencies since their immune system is altered, this surveillance is less effective and there is a greater chance that it will develop.

Unfortunately cancer seeks mechanisms from the beginning to evade the immune system, so that in some cases it finally manages to escape control and grow while avoiding the immune response. There are two major groups of mechanisms that the tumor uses to evade the immune system, avoid being recognized or produce immunosuppressive substances. Every day we understand better the mechanisms used by cancer to avoid the immune system so we can develop drugs aimed at these mechanisms and get the immune system to control the tumor again.

008  | Cart-cells in leukemia and other hematologic malignancies

Julio Delgado González
Haematologist, Hospital Clínic, Barcelona, Spain

The use of allogeneic hematopoietic transplantation is considered a standard treatment for many patients leukemia and many other hematologic malignancies. Unfortunately, this procedure has many drawbacks such as the need for an HLA-matched donor and long-term immunosuppression, which is associated with considerable toxicity and opportunistic infections. Chimeric antigen receptor (CAR) cells can be manufactured from the patient's own T-cells and do not require immunosuppression nor myeloablative chemotherap/car/therapy. Several CAR constructs have been developed, and two of them (both targeting CD19) have been already approved by the FDA/EMA for patients with acute lymphoblastic leukemia and non-Hodgkin’s lymphoma. Moreover, CART cells are also effective against other diseases such as chronic lymphocytic leukemia and even myeloma. This treatment is effective, but also associated with very specific side effects such as the cytokine release syndrome and permanent B-cell aplasia, this requiring a close follow-up of these patients. Several mechanisms of resistance have been already identified, which have led to the development of novel CAR constructs (“armored” CARs), dual CARs and the combined use of CARs and conventional drugs. Despite all the advances achieved in this fast-developing field, several questions need to be addressed, including the sustainability of these cell therapy products.
Prescribing is one of the most frequent procedures doctors do in their professional lives and distinguishes them from other healthcare professionals. According to the WHO, rational prescribing has been defined as “the situation in which patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for a sufficient length of time, with the lowest cost to them and to the community” (De Vries TP, Henning RH, Hogerzeil HV, Fresle DA. Guide to good prescribing. Geneva: World Health Organization; 1994). Rational prescribing is a challenging task and to accomplish with this objective several competencies have to be achieved, starting at the undergraduate level, to prevent the adverse consequences of poor prescribing. Prescribing competencies encompasses not only knowledge, but also skills and attitudes. And the acquisition of these competencies should be organised under the supervision of an expert on this field, that is, the clinical pharmacologist. In order to know the current situation of the Pharmacology, Clinical Pharmacology and Therapeutics learning in Spanish schools of medicine, a questionnaire survey was distributed among the professor in charge for the subject of Pharmacology at the Spanish schools of medicine in 2014. Twenty-two (65%) of the 34 schools of medicine responded. All the schools had a course in “Basic Pharmacology (BP)” taught mainly in the 3rd course of the curricula. The mean number of teaching hours received by the students was 69.2 h (SD: 15; min: 45; max: 96). The proportion of teaching hours given by teachers of different specialties varied extremely between the different schools but in 50% of them there were no clinical pharmacologists involved. A total of 90.5% of the schools had a formal course on “Clinical pharmacology (CP)”. However, “Therapeutics (T)” was only included in 42% of cases under this subject. This course was mainly taught during the fifth course of the curricula (52.6%). The mean number of teaching hours received by the students was 46.1 h (SD: 19; min: 14; max: 84). The proportion of teaching hours by teachers of different specialties varied extremely between the different schools but clinical pharmacologists were responsible for the majority of teaching in only 54% of the faculties answering this question. This survey revealed that the learning of BP is present in all the schools of medicine in Spain. However, there is a wide variety in the number of teaching hours of CP and of T as well as on the speciality of the teachers involved. In addition, currently there are no acknowledged requirements on key learning outcomes for undergraduate CPT education. To fill this gap the Education Working Group of the EACPT performed a modified Delphi study with the participation of 129 experts from 27 European countries who agreed on 252 learning outcomes to be included in undergraduate CPT curricula to ensure that European graduates are able to prescribe safely and effectively. These learning outcomes could be the reference to review and improve the teaching of CPT in Spain. Besides this discussion, the major challenges we, as the Spanish Society of Clinical Pharmacology, have to deal with is ensure that the experts guiding this learning process are clinical pharmacologists and that the trend towards integrated curriculums will prevent the CPT from losing visibility in the curricula.

In our country the number of outpatient hospital medicines, i.e. those that are dispensed by the hospitals’ pharmacy, has continuously increased in the last few years. This means that the number of patients attended to has also increased as well as hospital expenditure on these medicines. In fact, their percentage in the total hospital medicines expenditure has continuously increased in the last few years. In our hospital, outpatient hospital medicines expenditure was 90% of the total pharmacy expenditure in 2017 and the highest expenditure was on antineoplastic medicines, followed by immunosuppressants, antihemophilic medicines, anti-HIV medicines and medicines for multiple sclerosis. At the end of 2014 a committee for specific outpatient hospital medicines was created in our hospital with the following objectives: (1) give support to hospital managers on clinical and budget management of outpatient hospital medicines expenditure; (2) promote measures in order not to exceed the outpatient hospital medicines’ budget, and (3) promote clinical management measures in outpatient hospital medicines for some selected clinical services. It was an initiative taken by hospital managers, and the committee is composed of three hospital managers,
Clinical Pharmacology in Primary Healthcare (PHC) has mainly been developed in the hospital setting and there have only been some initiatives at PHC level in Mallorca, Galicia, Catalonia and others which have not always lasted.

Clinical pharmacologists in PHC develop their skills in a similar way to other healthcare settings and the main differences are due to the characteristics of the PHC, which includes a large spread of centres with many different professionals (family doctors, paediatricians, gynaecologists, nurses, etc.) with a very important assistance pressure and various types of activities, especially the preventive ones. These professionals are responsible for medicines conciliation for patients’ treatments prescribed in PHC or in specialized care, so the contribution of the clinical pharmacist in advising on new medications and in resolving consultations, sometimes urgently since the patient is in the consultation, is crucial.

All the work carried out by the clinical pharmacist in PHC aims to improve the quality of medicines use, maximising the benefit and minimising the risks, but also taking into account the sustainability of the system. The PHC mainly provides closeness to the patient in a more global way, from the approach of all their ailments and being aware of their family and social context. PHC includes healthy patients, where preventive actions are implemented, and pluripathological and polymedicated patients who require greater attention and, in many cases, home care.

To this end, actions aimed at increasing the safe use of medicines by providing tools to be incorporated into electronic health records (aids, warnings of interactions or contraindications, detection of duplications, etc.) are of particular interest. Other actions are aimed at improving the selection of medicines or withdrawing unnecessary treatments, both globally and individually, by analysing prescription profiles together with physicians and collaborating with them in medicines conciliation in polymedicated patients.

One of the main contributions of PHC is the collaboration with hospital professionals. PHC pharmacologists are members of therapeutic commissions of the reference hospitals; they collaborate in the elaboration of protocols and clinical practice guidelines jointly between both care environments and in the coordination between care levels for their implementation.

In addition to healthcare and management activities, we should not forget the training and teaching activities that are carried out periodically in PHC centres with subjects proposed by them or aimed at optimising aspects related to...
the treatment of prevalent conditions or diseases with significant therapeutic uncertainties.

We should not forget either the Research, which in PHC must be close to the usual clinical practice, from clinical trials to prospective observational studies that allow the inclusion of a large number of patients with low follow-up losses, although the scenario of high healthcare demand is not always favourable for carrying it out. The pharmacologist takes part in the different research phases from advising on the elaboration of the protocol, helping in its execution and collaborating in the discussion of results.

In recent years, electronic databases have been created, mostly from PHC electronic records. Our knowledge of how these records are collected makes it easier for us to plan studies on the drugs use in real clinical practice conditions, on adherence and persistence to treatments, and on assessing the relationship between drug use and clinical outcomes. This data can be obtained faster and more dynamic improvement actions can be proposed.

Definitely, our contribution to improving the quality of drug use in PHC is varied and important, although we are not always allowed to fully develop it.

CLOSING SEMINAR

012 | New challenges in drug evaluation and drug selection

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The main outcome of the drug development process should be a reasonable amount of evidence, able to support regulatory decisions on how to use new medications and allowing to estimate the benefits and risks of the intended use of the drug. Also, the gathered data should be informative enough as to define the ideal therapeutic positioning of the innovative product, in relation to already existing alternatives.

With almost one hundred new positive opinions being issued yearly by EMA in last years (one third for new chemical entities), good news is that the innovation crisis seems to be over. New types of products and targets are reaching the market, including paradigm-breaking approaches such as advanced gene and cellular therapies. A welcomed number of new orphan medicinal products become increasingly available, and the development of refined approaches based on molecular biology allow personalized targeting of disease with precise treatments limited to those patients who are suitable to receive them. In parallel, the way new drugs are studied and developed has changed, raising new challenges at the time of drug evaluation.

On one side, targeted treatments for molecularly refined medical indications lead to smaller and selected populations to be treated. As a consequence of lower prevalence of new conditions, conventional clinical developments become unfeasible since small samples limit statistical power. Thus, drug evaluation requires inference on efficacy from a limited amount of experimental data, that also deviates from the usual ICH-E1 standards leading to uncertainty also on risk assessments. Further, gene or cellular therapies are extremely targeted, and often a single administration is expected to have effects lasting years or being life-long. Whether relatively short term effects may be good predictors of efficacy – and safety – in the long term is often based on substantial extrapolation.

Rapidly evolving innovation is accompanied by new technologies and methodologies. Drug evaluation in this setting requires increasing levels of inference based on decreasing amounts of data, and a constant updating on scientific advancements with few clinical antecedents. Considering the potential impact and the degree of uncertainty, prudent evaluation seems a sensible advice. However, in the era of information, social and scientific expectations ask for innovation, and avoidance of any undesired delay in drug access for patients with unmet medical needs.

Since companies generally build the case of unmet need for their innovative products, fast-tracked regulatory and reimbursement decisions are normally claimed. In a context of unmet medical need and scarce data, the regulatory assessment of risk/benefit relies mostly on efficacy estimates, at the expense of safety uncertainties. Clinical emergency seems to justify early access, and safety information is delayed to post-commercialization phase. However, huge a priori expectations of benefit may not always be fulfilled by excellent results in clinical practice; then, by the time poor efficacy is concluded, the treatment has already been given to many of the potential candidates, posing a difficult problem to manage.

Finally, pricing expectations of pharma companies for new products do not parallel increasing degrees of clinical uncertainty. Contrarily, low return of investment from smaller target populations and the degree of innovation are driving substantially growing pricing trends. Budget compensation by generic or biosimilar products is outweighed by the number of innovations.

Challenges arising from this scenario may be managed in a number of ways, including early input into clinical development of regulators and health technology agencies, implementation of new trial designs suited to study small populations, strategies to deal with uncertainty, designs aimed to understand added value to current alternatives, and innovative pricing and managed entry systems, amongst others.
SEFC 2018 – Oral Comunications

SECTION: A. CLINICAL TRIALS

CO01 | Non-commercial vs. commercial clinical trials: a retrospective study of the applications submitted to a research ethics committee (REC)

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Objectives: There is a need to support independent clinical research addressing relevant clinical questions. There are many difficulties in undertaking independent clinical research without support from the pharmaceutical industry. It is essential that the results of clinical trials (CT) are available to guarantee the social value of the research. The objective of this study is to analyze some design characteristics, the registry to CT public registers and the publication rate of non-commercial CT after the implementation of the European Directive (ED) in Spain, compared with those of CT sponsored by the pharmaceutical industry.

Methods: A retrospective observational study of the applications of drug-evaluation CT submitted from May 2004 to May 2009 to the REC of our hospital (University Hospital Vall d’Hebron [Barcelona, Spain]) was performed. The information was obtained from the REC database and from public registers (clinicaltrials.gov and EU-CTR). The statistical analysis was descriptive.

Results: A total of 809 applications of drug-evaluation CT were submitted and 16.3% were noncommercial. They were mainly phase IV, multicentre national, and unmasked, compared to the commercial CT that were mainly phase II or III, multicentre international, and double-blind masked. 63.8% of the commercial CT and 39.4% of the noncommercial CT were published in peer-review scientific journals. 91.7% of the commercial CT and 55.9% of the noncommercial CT were registered in the clinicaltrials.gov register.

Conclusions: The proportion of noncommercial CT submitted to REC is still low compared to commercial CT. Results of CT with a commercial sponsor are published in peer-review scientific journals and registered in public registers at a higher percentage in comparison with noncommercial CT. Clinical researchers, especially those of noncommercial CT, must make a greater effort in order to disseminate the results of their research as well as not to compromise the social value of CT.

CO02 | Risk categorization in paediatric clinical research: views of involved agents

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Objectives: The assessment of the risk in clinical trials in paediatric population, particularly those without direct benefit to the minor, constitutes a major ethical aspects to be considered during its design and evaluation. In 2009, data from a survey among researchers showed high variability in risk perception.

Aim: Analyse the opinions of involved agents regarding to risk level of different procedures in a trial without direct benefit in minors at different age groups, considering interviewees education and professional experience.

Methods: An anonymous on-line questionnaire was conducted (2014) among members of RECs and paediatricians. The respondents should categorize the risk of different procedures according to three levels: a) Minimal risk, defined as “probability of damage or injury is not greater than that derived from the daily activity or during a physical or routine psychological examination”, b) minor increase over minimal risk and c) more than a minor increase over minimal risk.

Results: A total of 241 answer were received, 218 (90%) of respondents were health professionals, 155 (56%) at the paediatric setting and 95 (39%) belong to REC. In general, for all procedures the perception of the increased risk was greater in early ages (mainly up to 24 months); all procedures were categorized at the top of risk for more than 50% respondents in preterms, regardless their profile. The greater differences among paediatricians and REC member’s views were observed for two procedures. Allergy skin-test was...
perceived as minor risk among paediatricians vs REC members (4.5 vs 15.8% considering more than a minor increase over minimal risk); in contrary of hypoglycaemia test considered as greater risk among paediatricians (22 vs 35%)

**Conclusions:** Risk categorization is variable and depends of the professional experience. It seems necessary to enhance the training of the agents involved in the development and assessment of paediatric research in order to homogenize criteria.

**CO03 | Immediate: Results of a phase IIIb, open label randomised clinical trial to compare pain relief between methoxyflurane and standard of care analgesia for treating patients with trauma pain in spanish emergency departments**

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**Objectives:** To evaluate efficacy and safety of low dose methoxyflurane self-administered by the patient through a hand-held inhaler (MEOF) compared with the standard of care (SoC) in adult patients with trauma pain attending emergency departments in Spain.

**Methods:** In MEDIATE is a phase IIIb, randomized, open label, parallel group trial, conducted in 14 emergency departments. A total of 310 patients, with moderate to severe pain secondary to trauma, were randomized to receive either MEOF or SoC. The primary endpoint was the change in mean pain intensity from randomization to 3, 5, 10, 15 and 20 minutes after treatment administration and time to first pain relief. Adverse events were also evaluated. The trial was designed by members of SCReN (Spanish Clinical Research Network) and the Pain Working Group of SEMES (Spanish Society of Emergency Medicine). Management and monitoring were coordinated by SCReN. The sponsor and funder was Mundipharma Pharmaceuticals S.L.

**Results:** 156 in the MEOF group and 149 in the SoC one were included in the ITT analysis. Baseline characteristics were comparable between the groups. The mean age was 45.3 in both groups and initial NRS was 7.6 ± 1.4 (MEOF) and 7.5 ± 1.5 (SoC). In SoC group 88.9% of patients were treated with first-step analgesics +/- coadjuvants and 9.4% with iv/tm opioids. MEOF reduced pain severity significantly more than the SoC (P < 0.0001) at all time-points, with the greatest estimated treatment effect (adjusted from baseline) seen at 15 min after the start of treatment. Mean time to first pain relief was 5, 52 min in MEOF group vs. 11, 47 min in the SoC group (P < 0.001). MEOF was well tolerated, with the majority of adverse reactions being mild and transient and related with the pharmacological action.

**Conclusions:** Results indicate that methoxyflurane is an efficacious, well tolerated and rapid-acting analgesic that could be useful in Spanish emergency departments.

**CO04 | Strength of evidence of the efficacy of cholinesterase inhibitors for Alzheimer’s disease: A cumulative meta-analysis and trial sequential analysis of randomized placebo-controlled clinical trials**

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**Objectives:** To determine whether (1) the findings on the efficacy of cholinesterase inhibitors (ChEI) for Alzheimer’s disease are conclusive, and (2) the time point from which further research is redundant.

**Methods:** A systematic review, cumulative meta-analysis and trial sequential analysis (TSA) of randomized placebo-controlled clinical trials (RPCCT) that have studied the effect of donepezil, galantamine or rivastigmine in patients with AD were performed. The study outcome was the efficacy on global change, expressed as the number of patients who responded to the intervention. The odds ratio (OR) with 95% confidence interval was calculated for each study and a cumulative meta-analysis was performed. A relative risk reduction of 30% was considered the minimum clinically important difference. Required information size (RIS) was calculated. Both adjusted statistically significant and futility boundaries were constructed and the cumulative z-score of the efficacy was plotted.

**Results:** Twenty-one RPCCT published between 1998 and 2017 were included; 9 studied donepezil, 6 galantamine and 6 rivastigmine. The response rate was higher with ChEI than placebo (donepezil, OR = 2.19 [1.09-2.15]; galantamine, OR = 1.55 [1.24, 1.93]; rivastigmine, OR = 1.53 [1.09, 2.15]). The RIS was 1215, 908 and 1881 for
donepezil, galantamine and rivastigmine. Statistically significant heterogeneity was found for rivastigmine. The adjusted statistically significant boundary was crossed with the first RPCCT and before the RIS was reached for both donepezil and galantamine in 1998 and 2000, respectively. Rivastigmine showed fluctuant cumulative z-score that occasionally crossed the adjusted statistically futility boundary.

Conclusions: There is conclusive evidence on the efficacy on global change since the first pivotal RCCT of donepezil and galantamine published in 1998 and 2000, respectively. Therefore, redundancy research in the evaluation of efficacy on global change has been identified. Regarding rivastigmine, the strength of the evidence is fluctuant probably due to heterogeneity.

CO05 | Safety, tolerability and pharmacokinetics of single and multiple doses of ORY-2001, an epigenetic drug targeting LSD1 and MAO-B

Rosa M Antonijoan Arbós; Juan Manuel Ferrero-Cafiero; Joan Martínez-Colomer; Cesar Molinero; Cristina Marcaró; Maria Isabel Arévalo; Tamara Maes; Carlos Buesa

Objectives: To present the results of early investigations in healthy subjects on safety, tolerability (AEs) and pharmacokinetics of ORY-2001.

Methods: This First in human (FIH) study involved two stages, a single ascending (SAD) dose in healthy male volunteers and a multiple ascending dose study in healthy male young and elderly population (MAD). All studies were single-centre, randomized, double blind and placebo controlled. Within each cohort, 8 volunteers were incorporated gradually in the SAD and MAD. Tolerability was evaluated and plasma pharmacokinetics were studied.

Results: 40 healthy young male volunteers were included in the SAD study, 48 male and female and 4 elderly volunteers were included in the MAD study. No SAEs were reported during all studies.

SAD study: No differences between the active treatment and placebo in the subjects reported AEs were observed. The most common AE reported was headache.

MAD study: AEs related to the study medication showed no dose proportionality, and none was severe. The 4.0 mg/day dose produced a transient decrease in platelet count following a 5-day treatment period. There was no effect on other haematological parameters.

Safety and tolerability at 2.5 mg/day was similar in the elderly cohort.

ORY-2001 showed a rapid oral absorption tmax @ 2 h, relatively long half life @ 22 h, and dose proportional exposure. The concentrations appeared slightly lower in the elderly population and the difference increased as steady state was approached.

Conclusions: ORY-2001 showed a good safety and tolerability profile after administration in single or 5-day multiple doses. The most common AE reported during administration was headache. The subjects who received the highest dose 4 mg/day reported a transient platelet impact, and consequently, the MTD was 2.5 mg/day.

Pharmacokinetics profile shows lineal behaviour at the studied doses. These results support its further Phase II development in neurodegeneration and neuroinflammation.

CO06 | Effect of clarithromycin resistance and CYP2C19 polymorphism on the efficacy of therapies for helicobacter pylori infection in chilean people: Cohort study

Luis Rojas Orellana; Alex Arenas; Arnoldo Riquelme; Carolina Serrano; Luis Quiñones; Paul Harris; Mauricio Sandoval; Maria Lavanderos; Andres Jorquera

Objectives: The eradication of Helicobacter pylori (HP) is closely related to the prevention or treatment of gastric disease. The eradication resulting from standard triple therapy are mainly influenced by bacterial susceptibility to antimicrobial agents and the magnitude of the inhibition of acid secretion. The eradication rate has declined due to increasing resistance to clarithromycin (CR), but could also be affected by availability related to the proton pump inhibitor, which is due to part to the CYP2C19 polymorphisms. There are inconsistent studies on the roles of this polymorphism according to resistance to clarithromycin.

Our objective is evaluate the effects of CYP2C19 polymorphisms on the eradication rate of HP infection in Chilean adults with clarithromycin resistance.

Methods: Prospectively, 90 patients were recruited and assigned to 14 day regimens of therapy with omeprazole (20 mg), amoxicillin (1 g) and clarithromycin (500 mg), twice daily. All diagnoses of HP infection were based on a rapid urease test. Gene polymorphisms and antimicrobial
susceptibility were determined using Real time PCR system and molecular assessment by PCR-RFLP, respectively.

**Results:** The eradication rate resulting was 69.4%. The rate of CR was 22.2%. The frequency of polymorphism were: ultrarapid metabolizer (UM):6.7%; extensive metabolizer (EM): 77.8%; intermediate metabolizer (IM):15.5%; poor metabolizer (PM):0%. The genotypes were classified into the two groups for evaluate their effects: UM+EM and IM. The eradication was lowest in patients with CYP2C19 UM+EM/clarithromycin resistance (27.8%) and highest in UM+EM/ clarithromycin susceptibility (83%) (P < 0.001).

**Conclusions:** Clarithromycin resistance had a synergistic effect with CYP2C19 UM+EM on regimen efficacy. In a population with a high rate of clarithromycin resistance it could be useful to know the CYP2C19 polymorphism to choose other therapeutic schemes that consider higher doses of omeprazole or inhibitors of the proton pump less affected by CYP2C19 polymorphisms, such as Esomeprazole or Rabeprazole. Studies with high simple size are needed to verify this conclusion.

**SECTION: B. PHARMACOKINETICS, PHARMACOGENETICS/PHARMACOGENOMICS**

**CO07 | Therapeutic drug monitoring of anti-tnf therapy in crohn’s disease is mainly influenced by systemic inflammation**

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**Objectives:** Serum free anti-TNF monitoring to optimize biological treatment is controversial due to the high variability observed. Our objective was to identify genetic, inflammatory, clinical and analytical parameters that better explain the variability observed in Crohn’s disease (CD) patients.

**Methods:** CD patients followed at our hospital either on regular or intensified schedules of anti-TNF therapy with infliximab or adalimumab at stable doses at least for three months were included. Clinical and analytical data were recorded. Patients were genotyped for genes associated with inflammation and autophagy. Serum cytokine and anti-TNF drugs levels were measured in serum taken just prior to infusions. U Mann-Whitney and linear regression tests were performed using the R software (v3.2.3).

**Results:** 112 CD patients with anti-TNF (62 on infliximab and 50 on adalimumab) were included. Fourteen patients on infliximab (22.5%) and 15 on adalimumab (30%) were receiving an intensified regimen (P = 0.37). No significant differences were found in clinical characteristics according to intensified vs non-intensified regimen, regardless of biological drug used. Similar anti-TNF trough levels were observed in patients treated with infliximab (5414.4 ± 2336.6 ng/mL) or adalimumab (5612.9 ± 2116.8 ng/mL, P = 0.64). Despite higher doses administered the intensified patients showed anti-TNF levels (5154.9 ± 2416.9 ng/mL) lower than expected and similar to those showed by patients on regular schedule (5624.6 ± 2167.9 ng/mL, P = 0.36). Intensified patients showed higher levels of inflammatory cytokines IL26 (78.3 ± 36.1 pg/mL vs 35.3 ± 32.4 pg/mL, P < 0.0001) and TNF (86.4 ± 15.3 pg/mL vs 66.1 ± 31.1 pg/mL, P < 0.0001) and lower levels of anti-inflammatory cytokine IL10 (35.1 ± 23.7 pg/mL vs 40.0 ± 22.3 pg/mL, P = 0.044). In the multivariate analysis controlled by weight, type of anti-TNF and regimen, IL-10 was the best fitting variable associated with anti-TNF through levels variability.

**Conclusions:** Serum cytokine IL10 is the parameter that best explain anti-TNF trough levels variability in CD patients. Systemic inflammatory load in CD patients should be taken in consideration in the design of future studies of anti-TNF therapeutic drug monitoring.

**CO08 | Utility of therapeutic drug monitoring in chronic myeloid leukemia: A systematic review**

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**Objectives:** Therapeutic drug monitoring (TDM) in chronic myeloid leukemia (CML) is the measurement of tyrosine kinase inhibitor (TKI) plasma concentration to predict efficacy and safety outcomes. It could help the physician to take decisions when molecular response is not achieved or when adverse reactions are present. This study aims to examine the utility of imatinib, nilotinib and dasatinib TDM in adult chronic-phase CML patients. TDM would be deemed useful if it is able to detect groups of patients with opposite clinical outcomes measuring plasma TKI concentrations. This should allow to define a therapeutic range for each TKI.

**Methods:** A systematic review of studies reporting TKI trough levels (C_{min}) and clinical outcomes was performed. We calculated the difference of mean C_{min} between patients achieving and not achieving major molecular response, and between patients presenting and not presenting adverse reactions. Meta-analyses, Student-t tests and ROC analyses were employed to detect mean differences between groups and optimal cutoff concentration values.
**CO09 | Effect of Roux-En-y Gastric Surgery on ciprofloxacin pharmacokinetics: An obvious effect?**

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**Objectives:** To evaluate bioavailability pharmacokinetic parameters of ciprofloxacin in patients undergoing Roux-en-Y gastric surgery (RYGS).

**Methods:** Single-dose, open-label, cross-over bioavailability study in patients undergoing RYGS and control subjects (body weight-paired to +6 month post-surgery patients). Healthy overweight/obese patients 18-60 years old were included. The assessment was performed once in Control patients and three times in Case patients (before, +1 and +6 months after surgery). In each visit, after overnight fasting, the subjects received a single oral dose of Ciprofloxacin 500 mg. Venous blood samples were obtained at baseline and 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 8 and 14 hours after Ciprofloxacin intake. Pre- and post-surgery variables were compared using paired ANOVA or Wilcoxon tests, and control vs. cases using ANOVA or Mann Whitney. Given the post-surgery change in body weight, parameters were corrected by dose (mg)/body weight (kg). The analysis was performed using WinNonlin and SPSS.

**Funding:** ISCIII ("PI11/01455"), co-funded by ERDF/ESF.

**Results:** 34 subjects completed the study (82.4% female). Ciprofloxacin Cmax was significantly reduced at +1 m after surgery (1840.9 ± 485.2 vs 1589.6 ± 321.8 ng/mL; \( P = 0.032 \)) though not at +6 m. Cmax at +6 m cases was lower than in Control group (2160.4 ± 408.6 vs 1589.6 ± 321.8 ng/mL; \( P < 0.001 \)). After correcting by the dose (mg)/patient's body weight, both Cmax and AUClast showed significant decreasing at +1 and +6 m after surgery (Cmax: 289.1 ± 65.3 and 263.5 ± 52.1 (ng/mL)/(dose (mg)/weight (kg)) respectively, vs 429.3 ± 127.6 (ng/mL)/(dose (mg)/weight (kg)) at baseline; AUC:1340.6 ± 243.0 and 1299.2 ± 415.4(h*ng/mL)/(dose (mg)/weight (kg)) respectively vs 1896.7 ± 396.8 (h*ng/mL)/(dose (mg)/weight (kg)) at baseline. Cmax at +6 m post-surgery showed lower values than the control group (375.4 ± 77.4 vs 263.5 ± 52.1 ng/mL; \( P < 0.001 \)), however, no statistically significant difference was detected at 6 months in AUC.

**Conclusions:** Ciprofloxacin absorption is impaired at +1 m and +6 m after RYGS. The effect on Cmax and AUClast are faded at +6 m due to weight loss. It is unlikely the need of modifying the doses of Ciprofloxacin in this patients.

**SECTION: C. PHARMACOVIGILANCE, SAFETY AND QUALITY**

**CO10 | Clopidogrel shares with low-dose acetylsalicylic acid a comparable protection against colorectal cancer: A population-based case-control study**

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**Objectives:** The mechanism of action of low-dose acetylsalicylic acid (ASA) to explain its chemopreventive action on colorectal cancer (CRC) is still debated. Some evidence suggests that the antiplatelet effect of low-dose ASA (through irreversible inhibition of platelet-COX-1) might be the principal mechanism. This platelet hypothesis would be reinforced if other antiplatelet agents, acting through a mechanism of action unrelated to COX-1 as clopidogrel, would present a comparable effect to low-dose ASA.

**Methods:** A case-control study nested in a primary cohort selected from the Spanish primary care database BIFAP between 2001 and 2014. Individuals aged 20-89 and without previous history of cancer were followed-up until an incident CRC record (index date), other cancer record, 90 years, death or end of study. 15,491 incident CRC cases were detected and validated and 60,000 controls were randomly selected.
CO11 | Risk of myocardial infarction and use of calcium-supplements in monotherapy and in combination with vitamin D: A population-based case-control study

Sara Rodríguez-Martín; Diana González-Bermejo; Antonio Rodríguez-Miguel; Diana Barreira Hernández; Jose Alberto García-Lledó; Miguel Jesús Gil García; Francisco Jose De Abajo Iglesias

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Objectives: To test the hypothesis that use of calcium supplements, either in monotherapy (CaM) or in combination with vitamin D (CaD), is associated with an increased risk of acute myocardial infarction (AMI).

Methods: We performed a case-control study nested in a primary cohort selected from the Spanish primary care database BIFAP between 2002 and 2015. Individuals aged 40-99 and without a previous history of cancer and AMI were followed-up until an incident AMI record, a cancer record, 100 years old, death or end of study period. A total of 24 155 incident AMI cases were identified and validated; 5 controls per case were randomly selected from the underlying cohort using a risk set sampling and matched to cases by age, sex and index date (the date of AMI diagnosis). Exposure to drugs were classified as current (0-30 days prior index date), recent (31-365 days), past (>365 days) and non-use (no prescription record). Odds ratios (OR) and 95% confidence intervals (CI) were computed using a conditional logistic regression adjusted for potential confounders.

Results: Current use of clopidogrel monotherapy presented a reduced risk of CRC; AOR = 0.80 (95% CI: 0.69-0.93) and 0.65 (0.55-0.78) after 1 year of treatment. This effect was maintained by age and sex. Current use of low-dose ASA was associated with an AOR of 0.83 (0.78-0.89) and 0.79 (0.73-0.84) for periods longer than 1 year. Dual antplatelet therapy presented a similar effect than the one observed among single users of each antplatelet drug.

Conclusions: The use of clopidogrel was associated with a risk reduction of CRC, duration-dependent and similar in magnitude to the one observed among users of low-dose ASA, giving support to the antplatelet action as the main mechanism behind their chemopreventive effect on CRC.

SECTION: D. DRUGS UTILIZATION STUDIES, PHARMACOECONOMICS

CO12 | Potentially inappropriate medications (PIM) in the elderly: Project to create a Spanish list (ES-PIA PROJECT)

Maria Del Mar García Sáiz; Magali González-Coloa Harmand; Ana M. Aldea Perona; Consuelo M. Rodríguez Jiménez; Carlos Boada Fernández Del Campo; Candelaria Grillo Grillo; Paula Masiero Aparicio; Andres Orellana Mobilli; Eduardo Fernandez Quintana; Marcelino García Sánchez-Colomer; Mercedes Plasencia Núñez

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Objectives: To establish a list of potentially inappropriate medications (PIM) in the elderly, the reasons for inappropriate prescription and supporting evidence.

To provide an updated tool adapted to Spanish market, designed to support prescription programs in the elderly.

Methods: The Delphi-method was used, and successive steps were followed: (1) Formulation of the problem; (2) Selection of a coordinator team of 12 experts (Clinical Pharmacology, Geriatrics, Rational Drug Use, Primary Care, Pharmacopidemiology-Farmacovigilance); (3) Creation of a preliminary questionnaire of IM based on the review of publications, Summary of Products Characteristics (SPC) of each drug, and safety warnings of Spanish Medicines Agency; (4) Recruitment of 25 independent experts from different
backgrounds and geographic areas of Spain; (5) Mailing of two rounds of questionnaires. In each round, the experts were asked to give their agreement with the statements proposed using a 10-point Likert-scale, and their reasons; (6) Elaboration of a final IM prescription list adapted to the Spanish pharmacopoeia, and applicable in people over 65 years.

Results: 1462 SPC were reviewed. A list of 160 sentences, in the form of statements (e.g. “Antiepileptics in the elderly increase the risk of confusion, syncope, ataxia or alterations in psychomotor function”), was reviewed by the coordinator team and proposed in the first round questionnaire. A high degree of agreement was reached in 108 sentences (106 accepted; 2 rejected), 22 had low agreement, and 32 medium agreement. These 32 sentences passed to a second round, and in all of them, high agreement was reached. Finally, 138 sentences were accepted. Response rate was 100% in both questionnaires.

Conclusions: This project has allowed to develop a list of PIM in the elderly, supported by high degree of agreement in a large multidisciplinary team. The list will be published since it can be used as a tool to support prescription.

CO13 | Increased prescribing trends of psychotropic medicines in Spanish paediatric population: Sensation, perception or reality

Belén Ruiz-Antorán1,2; Laura Javaloyes3; Ana Ascaso del Rio2; M. Inmaculada Palanca Maresca3; Gustavo Centeno1; Arantxa Sancho-López1; Angela Izquierdo3; Pablo del Sol3; Cristina Avendaño-Solá1,2

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Objectives: To describe the profile of use of psychiatric medicines in the paediatric population in specialized health care and its evolution from 2011 to 2017.

Methods: Observational, longitudinal, retrospective drug-utilization study. All patients with electronic medical records and attended at the paediatric Northwestern mental health area of Madrid between 2011 and 2017 were included. The exposure to the psychotropic drugs was considered per patient-year(s).

Results: A total of 7070 patients (1011 patients-year) were included, 64% males, mean age 11.4 + 4.1. The longitudinal analysis showed a progressive increase in the percentage of patients receiving treatment with some psychotropic medicines, from 53.1% in 2011 to 72.5% in 2017. By age subgroups, this increase was observed across all groups: 0-6 years: 3.4% to 12.9%; 6-12 years: 46.8% to 66.2%; 12-18 years: 60.7% to 83%. There is an increase in the prescription of stimulants (50.2-71.5%) and antidepressants (15.2-28.8%) (Table 1).

In relation to the concomitant use of medicines, the percentage of patients with more than one psychotropic medication from different therapeutic groups increased from 12% in 2011 to 30% in 2017. Up to 49% of treated patients received additional psychological treatment and this percentage remained stable over the years.

Conclusions: The use of psychotropic medicines in the paediatric population attended at Psychiatry Units has increased in recent years. There is an increase in stimulants and also an increase in antidepressants, possibly related to a broadening of indications. Only half of children treated pharmacologically received concomitant psychological treatment, which is far below our expectations.

<table>
<thead>
<tr>
<th>% of patients treated with any psychotropic-medication (%)</th>
<th>Antipsychotics (%)</th>
<th>Anxiolytics /Hypnotics (%)</th>
<th>Antidepressants (%)</th>
<th>Stimulant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 46.0</td>
<td>27.5</td>
<td>26.2</td>
<td>23.6</td>
<td>50.2</td>
</tr>
<tr>
<td>2012 53.1</td>
<td>19.3</td>
<td>25.5</td>
<td>33.9</td>
<td>50.5</td>
</tr>
<tr>
<td>2013 53.3</td>
<td>21.4</td>
<td>18.1</td>
<td>32.7</td>
<td>57.9</td>
</tr>
<tr>
<td>2014 66.9</td>
<td>21.0</td>
<td>14.7</td>
<td>32.9</td>
<td>64.0</td>
</tr>
<tr>
<td>2015 69.8</td>
<td>25.2</td>
<td>17.4</td>
<td>40.1</td>
<td>62.4</td>
</tr>
<tr>
<td>2016 72.3</td>
<td>23.3</td>
<td>17.6</td>
<td>36.1</td>
<td>64.3</td>
</tr>
<tr>
<td>2017 72.5</td>
<td>18.9</td>
<td>12.0</td>
<td>28.8</td>
<td>71.5</td>
</tr>
</tbody>
</table>
CO14 | Concomitant use of psychotropic drugs in attention deficit hyperactivity disorder (ADHD)

Belén Ruiz-Antorán1; Laura Javaloyes1; M. Inmaculada Palanca Maresca2; Gustavo Centeno1; Miguel Vizcaíno3; Roberto Fernández2; Concepción Payares Herrera1; Cristina Avendaño-Solá1

1Servicio Farmacología Clínica, Hospital Universitario Puerta de Hierro-Majadahonda, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana, Madrid, Spain; 2Unidad de Psiquiatría del Niño y el Adolescente, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

Objectives: To describe the profile of current drug therapy use in paediatric patients diagnosed of ADHD in specialized health care and its evolution from 2011 to 2017. To analyse the concomitant use of medicines associated with stimulants for the treatment of ADHD with/without psychiatric-comorbidity.

Methods: Retrospective, longitudinal drug utilization study. We included all patients with electronic medical records, seen at the paediatrics Northwestern mental health area of Madrid, between 2011 and 2017 with a diagnosis of ADHD (ICD10: F90.0–F90.9).

Results: Of the 7070 pediatric patients attended in the Mental Health Area, 3416 with ADHD, 44% had associated psychiatric-comorbidities. The analysis showed a progressive increase in the percentage of patients diagnosed, from 28.4% (2011) to 59.6% (2017). The percentage of ADHD with psychiatric-comorbidity remained stable.

The overall percentage of treated patients increased from 74% (2011) to 87% (2017). There were no significant differences in relation to patients who had associated comorbidity (2017: 86.2% vs. 86.9%). The frequency of prescription for each pharmacological group is shown in Table 1.

Conclusions: The diagnosis of ADHD has increased between the years 2011-2017. The percentage of ADHD patients with pharmacological treatment remained stable. There is concomitant use of other psychotropic drugs, particularly antidepressants and antipsychotics, in a 6-8% percentage of ADHD patients without other psychiatric diagnoses.

SECTION: E. CLINICAL PHARMACOLOGY TEACHING, OTHER ISSUES

CO15 | Experience and participation of clinical pharmacology in the assessment of clinical competences in medicine using an objective structured clinical examination “OSCE”

Encarnación Blanco Reina1; Elisa I. Márquez Romero1; Inmaculada Bellido Estévez1; Judith Sanabria2; Mª Rosario Cabello Porras1; Juan Antonio García Arnés3; Pedro Valdivielso Felices4; Mª Isabel Lucena González1,2

1Dpto. Farmacología, Facultad de Medicina, Universidad de Málaga, IBIMA, Málaga, Spain; 2S. Farmacología Clínica, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain; 3Hospital Provincial de Málaga; 4Hospital Clínico Universitario Virgen de la Victoria, Dpto Medicina, Facultad de Medicina, Universidad de Málaga, IBIMA, Málaga, Spain

Objectives: The Objective Structured Clinical Examination “OSCE” was designed to assess student’s clinical competence and currently it is necessary to pass it before finishing the degree of Medicine. The aim of this work has been to assess the results of different clinical pharmacology stations in the OSCE pregraduation in Medicine during 2016-2018.

<table>
<thead>
<tr>
<th>% of patients without treated comorbidity</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants*</td>
<td>83.0</td>
<td>89.3</td>
<td>78.5</td>
<td>85.8</td>
<td>95.1</td>
<td>93.3</td>
<td>93.3</td>
</tr>
<tr>
<td>No Stimulants**</td>
<td>20.8</td>
<td>15.5</td>
<td>24.8</td>
<td>27.4</td>
<td>7.6</td>
<td>4.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>9.4</td>
<td>6.8</td>
<td>7.7</td>
<td>2.8</td>
<td>8.0</td>
<td>10.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Hypnotics/Anxiolytics</td>
<td>1.9</td>
<td>2.9</td>
<td>2.9</td>
<td>0.5</td>
<td>1.5</td>
<td>2.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Antidepressives</td>
<td>9.4</td>
<td>2.9</td>
<td>5.5</td>
<td>2.8</td>
<td>6.1</td>
<td>11.3</td>
<td>6.4</td>
</tr>
<tr>
<td>% of patients with treated comorbidity</td>
<td>2011</td>
<td>2012</td>
<td>2013</td>
<td>2014</td>
<td>2015</td>
<td>2016</td>
<td>2017</td>
</tr>
<tr>
<td>Stimulants*</td>
<td>70.9</td>
<td>72.6</td>
<td>63.5</td>
<td>80.4</td>
<td>82.5</td>
<td>81.4</td>
<td>84.4</td>
</tr>
<tr>
<td>No Stimulants**</td>
<td>25.5</td>
<td>22.6</td>
<td>24.6</td>
<td>30.1</td>
<td>6.6</td>
<td>8.8</td>
<td>19.7</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>20.0</td>
<td>21.7</td>
<td>30.5</td>
<td>30.1</td>
<td>27.9</td>
<td>18.9</td>
<td>21.6</td>
</tr>
<tr>
<td>Hypnotics/Anxiolytics</td>
<td>18.2</td>
<td>5.7</td>
<td>9.0</td>
<td>9.1</td>
<td>12.7</td>
<td>8.8</td>
<td>8.6</td>
</tr>
<tr>
<td>Antidepressives</td>
<td>20.8</td>
<td>25.1</td>
<td>31.5</td>
<td>45.4</td>
<td>30.9</td>
<td>29.0</td>
<td>17.7</td>
</tr>
</tbody>
</table>

*Methylphenidate-Lisdexamfetamine/**Atomoxetine.
Methods: We have organized three stations with clinical cases for prescribing and a station for parenteral drug administration. In the clinical pharmacology prescription stations students were presented a clinical case, laboratory data and medication used. They had to optimize the therapeutic plan and fill in on a model of common electronic prescription.

Results: The clinical cases were three different patients with a variety of comorbidities such as hypertension, diabetes, dyslipidemia, pain, urinary tract infection or impaired renal function. In the cases there were interactions, side effects, lack of efficacy, etc. We established 10 items that assessed clinical judgment and therapeutic management plan for each of the stations (except in parenteral administration, in which we value skills). In total, 665 students were examined so far in the hospital setting (Málaga). The average rating of the whole stations ranged between 3.6-8.9. Clinical pharmacology station reached 7.4 (range 1.5-10) in 2016, 6.4 (1-10) in 2017, and 4 (1-8) in 2018. The easiest items were pharmacodynamic interactions NSAIDs-antihypertensive, side effects of ACE inhibitors and antibiotic selection based on antibiogram. However, the correct choice of analgesia and the dose adjustment of drugs in renal insufficiency were the most difficult items.

Conclusions: The deficiencies found in the competences regarding clinical judgment and therapeutic management versus communication skills and abilities were an important finding. In prescribing, we have detected a dissociation between what students “know” with what they are “show do” or “do”. We must reflect on these results to guide the teaching of clinical pharmacology towards prescription skills.
ABSTRACTS

SECTION: A. CLINICAL TRIALS

CP01  | Analysis of the clinical trials initiated in the clinical trial unit of University Hospital Virgen del Rocío between January 2016 and April 2018

Alicia Marín Candón; Lucía Jiménez González-Serna; María Cala Martínez; Rocío Cidoncha Martínez; Antonio Cervera Barajas

Hospital Universitario Virgen del Rocío, Sevilla, Spain

Objectives: To evaluate the main characteristics of the clinical trials initiated in the Clinical Trial Unit of the University Hospital Virgen del Rocío.

Methods: We analyzed the clinical trials (CTs) currently active or not in our Unit between 1st January 2016 and 30th April 2018. We analyzed: number of CTs; medical specialty; phase of the trial; number of patients compromised; number of patients included; time taken to include the first patient and compliance obtained.

Results: 49 CTs were analyzed including 180 patients. The most involved medical specialty was Medical Oncology with 18 CTs, followed by Oncohematology (8 CTs) and Endocrinology (5 CTs). The 44.89% of the CTs were phase I.

Of 180 patients analyzed, 51 of them were screening failure, 52 patients were discontinued for progression disease or toxicity, 26 patients carried out all the visits and 51 patients were active at 30th April 2018. The total number of active patients at 30th April 2018 was 71, of which 20 patients belonged to CTs opened before 1st January 2016, and 51 patients included during the date analyzed.

Average time for inclusion the first patient were 87 days, although there were some CTs which inclusion time was 2-3 days.

In 11 CTs did not include any patients. Proportion of patients compromised/included was 42.85%. Medical Oncology included 91 patients (50, 55%) followed by Pediatrics with 19 patients (10.55%).

21 CTs reached the compliance of patients included.

Conclusions: Medical Oncology is the medical specialty with more CTs accomplished and more patients included, despite of the increased of CTs and patients included in Pediatrics these years.

It can be interesting to analyze the quantity of screening failure developed in these 16 months.

It must be emphasized the need of optimize the capacity of recruitment and time to recruit the first patient from the site visit.

CP02  | How many patients are involved in medical research? Are we truly minimizing the number of patients submitted to risks?

Pau Alcubilla Prats; Silvia Fernández García; Marina Rovira Illamola; Nuria Soler Blanco; Alicia Bernal Pérez; Albert Planas Sala; Cristina Rodríguez Arroyo; Neus Riba Garcia

Hospital Clinic Barcelona, Spain

Objectives: To perform an estimation of the total number of patients enrolled in any prospective clinical investigation in one year time in our Hospital.

Methods: We reviewed all studies approved by the Barcelona Hospital Clinic Research Ethics Committee during 2017. We included clinical trials with drugs, studies with medical devices, post-authorization studies with drugs (except retrospective) and other investigational biomedical projects. We recorded information about expected sample size, expected sample size of the control group (if any), the number of participating sites and issues about sample size calculation. With this data, assuming that each participating site contributed equally to patient recruitment, we estimated the expected number of participants that would have been enrolled in our center.

Results: A total of 1070 studies were revised. Of these, 581 were prospective studies with direct patient involvement and 53 studies were ruled out because of a lack of relevant information.

The total number of expected enrollment for prospective studies in our center is 33 544 participants with 3886 patients assigned to control group (11.58%). No sample size calculation was assessed in 203 studies (38.45%) which imply 56.35% of total patients.
Our center saw roughly 300 000 patients during 2017. Assuming that this number remains constant, and that the recruitment rate is the same throughout the years, we estimate an overall incidence of 11.18% patients/year (an estimated prevalence of 25%).

Conclusions: Our results show that the number of patients involved in prospective clinical investigations in our hospital is high, and many patients are enrolled in studies without formal sample size calculation. The Declaration of Helsinki states that in medical research, most interventions involve risk and burdens. Researchers should carefully assess how many patients to include in clinical investigations in order to avoid submitting too many subjects to potentially unnecessary risks.

CP03 | Gender differences on alcohol concentrations and effects in an experimental binge drinking episode

Clara Pérez Mahã; Lourdes Poyatos Blanco; Ramon Monfã Escolã; Soraya Martí Sanchez; Anabel Barriocanal Barriocanal; Susana Malumbres Serrano; Magí Farré Albaladejo; Esther Papaseit Fontanet

Hospital Universitari Germans Trias i Pujol (IGTP) – Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

Objectives: Binge drinking (BD) it has become trendy among adolescents and young adults. Binge drinking is defined as a pattern of drinking that reach blood alcohol concentration (BAC) to 80 mg/dL in a short period of time (2 hours) that typically occurs after 4 drinks for women and 5 drinks for men. The aim of this study was to evaluate the gender differences after the administration of alcohol simulating a BD episode under experimental conditions.

Methods: Eleven male and five healthy female volunteers, with previous BD behavior participated in one experimental session. They received an oral dose of 70 g of alcohol, mixed with zero orange soda without bubbles (Trina®) distributed in 6 glasses (total volume 900 mL) over a 2-hour period (20 minutes for glass). The trial was single-blind, non-randomized and non-controlled. Study variables included vital signs, subjective effects and BAC measured along 12 hours.

Results: Preliminary results showed a peak BAC of 127.55 ± 18.58 mg/dL in males and 159.60 ± 20.34 mg/dL in females. BAC remained higher than 80 mg/dL during 3 and 4 hours after alcohol administration, respectively. They experienced similar intensity of drunkenness and positive effects. Both, BAC and effects peaks were observed at 2 hours. Females displayed more intense negative effects than males.

Conclusions: The alcohol dose administrated in 2 hours produced a BD episode in both genders. Time course of BAC and alcohol pharmacological effects show a similar profile. However, females presented higher BAC and negative effects of alcohol than males. These preliminary results indicate that females could be more vulnerable to alcohol’s effects of binge drinking than males.

Acknowledgements: Ministerio de Sanidad, Política Social e Igualdad (Plan Nacional Sobre Drogas, 2016I024). Instituto de Salud Carlos III (Red de Trastornos Adictivos ISCIII-FEDER RD16/0017/0003; Esther Papaseit is a Juan Rodes fellowship ISCIII JR16/0002) Suport Grups de Recerca AGAUR Gencat (2017 SGR 316).

CP04 | Monitoring strategies for clinical trials in primary care: an independent clinical research perspective

Marta del Álamo1; Ana Isabel Sánchez1; Maria Luisa Serrano1; Mónica Aguilar1; Mireia Arcas2; Ángela Álvarez1; Laura del Olmo1; Itziar de Pablo1; Mª Angeles Galvez1

1UICEC Hospital Universitario Ramón y Cajal. SCReN, Madrid, Spain; 2UICEC Hospital Fundación Jimenez Díaz. SCReN, Madrid, Spain

Objectives: To describe the strategies implemented by Hospital Ramón y Cajal Clinical Trial Unit-SCReN to give regulatory and monitoring support to the first independent multicenter clinical trial (CT) in Primary Care (PC) in the Autonomous Community of Madrid (OB12).

Background: OB12 is a pragmatic, controlled, randomized, multicenter CT to compare the effectiveness of orally and intramuscularly administered vitamin B12 in the treatment of patients ≥65 years old with vitamin B12 deficiency involving 23 primary care centers and 191 investigators. Monitoring, pharmacovigilance and regulatory activities were supported by the non-commercial clinical trials platform SCReN. Several challenges/barriers were encountered on developing these activities.

- Limited budget
- Large number of investigators by site
- Limited previous experience of trial staff on randomized clinical trials
- Increased workload of trial staff
- Timing

Methods: We developed adapted monitoring approaches including:

- Adapted Initiation site visits: initiation activities for all sites were developed in two meetings adapted to regular primary care physicians’ schedule.
- Combined on site (OS) and on line (OL)/centralized monitoring visits. OL monitoring was made once at
least one OS visit has been made. The ratio OL/OS was adapted to trends uncovered during OS visits.

- Reduced essential documents files organization.

**Results:** Customized monitoring activities allowed us to perform and finish the clinical trial ensuring compliance with Good Clinical Practice (GCP). Combined OL and OS monitoring visits aimed to assure patients safety and data integrity with limited monitoring resources. Overall, OL monitoring was more effective for source data verification (SDV) than OS monitoring, especially in sites with a large number of investigators. Reduced trial files organization and initiation site visits aimed to overcome time and budget limitations.

**Conclusion:** Setting up a non-commercial, limited-budget, multicenter CT in PC requires customized monitoring strategies. The CT presented here is an example of primary care-adapted monitoring strategies supported by a SCReN clinical trials unit.

**CP05 | Use of the telephone interview as an effective method in the screening process (Nurse unit experience)**

Marta Perez Otero; Julian Mateus Rodriguez; Esther Menoyo Colmenarejo; Klaus Langorh; Rafael De la Torre

**IMIM, Barcelona, Spain**

**Objectives:** To demonstrate the effectiveness of using a quality telephone interview as a screening to recruit volunteers for clinical trials.

**Methods:** Twenty-three clinical trials were analyzed between the years 2006 and 2016 at the IMIM’s Clinical Research Unit Phase I (Institut Hospital de Mar d’Investigacions Mèdiques), a total of 1040 volunteers were contacted to join in the different clinical trials. The volunteers were filtered for first time through a complete telephone interview that consist in a set of standardized questions for all volunteers (age, sex, weight, usual prescription..) and a variable questions set that were asked depending on the inclusion criteria for each clinical trial. Two variables were analyzed: (1) Number of volunteers reviewed over those contacted. (2) Number of volunteers included compared volunteers checked at the medical screening visit. This data was extracted from de IMIM database.

**Results:** An analysis of proportions based on negative binomial distribution was carried out, with a 95% confidence interval that 91.8% of the volunteers who are screened by telephone are suitable for clinical trials and that 59.9% of the volunteers who are contacted are discarded thanks to the application of this tool.

**Conclusions:** The telephone interview has been an effective tool for the recruitment of volunteers in clinical trials, the high percentage of volunteers considered suitable evidence that it is a high-precision instrument, In accordance with the selection medical visit. It is considered a replicable option for different clinical trials units that could optimize resources and it would improve the selection process.

**CP06 | Participation of patients in clinical trials at the Ramon y Cajal Hospital Phase I Clinical Trial Unit: perception and degree of satisfaction**

Maria Angeles Galvez Mugica1; Jose Daniel San Andrés Muñoz2; Isabel Lopez Algarra2; Itziar de Pablo López de Abechuc2; Mónica Aguilar Jimenez2; Ana Isabel Sanchez Espada2; Marta del Alamo Camuñas2; Maria Luisa Serrano Olmeda2

1 Unidad de Farmacología Clínica Hospital Ramón y Cajal. IRYCIS. SCReN, Madrid, Spain; 2Hospital Ramón y Cajal, Madrid, Spain

**Objectives:** To know the patients’ perception/opinion and their degree of satisfaction regarding their participation on a clinical trial (CT). Secondary: to evaluate their opinion about the clinical trial’s staff and the degree of complexity of the trial.

**Methods:** We prepared a survey with 23 questions regarding subjects related to studies procedures, number of visits and its duration, adverse events etc. We asked them about their perception about the clinical trial’s staff assistance as compared with usual healthcare practice. In addition, the patients were asked whether they have considered withdrawing the trial and their reasons for doing it or not.

**Results:** 28 patients filled the survey. Participating in a CT is not more complicated than expected for the 86%. 40% had to go to the Emergency Department and only one patient said that it had been complicated because of CT. All patients have correctly complied with the trial procedures. 61% had been previously treated for the same pathology and, in these cases 70% consider that the treatment has been different from the usual practice. The biggest difference is about the improvement in the management of clinical tests. 86% did not need psychological support and 61% do not consider it necessary to have a psychologist as part of the study staff. They all have felt supported by their relatives but 25% consider that it has been somehow complicated for them. The physician is the clinical trial’s staff member preferred by patients to solve their doubts. 82% wish to receive information about the results of the trial and to be grateful for their participation. 75% prefer to receive this information directly from the physician.
Conclusions: Patients’ satisfaction with their participation in the EC is very high and everyone would recommend it to other patients.

CP07 | Role of the ethics committees for investigation (CEI) and ethics committees for investigation with medicinal products (CEIm) in follow-up activities on biomedical research studies

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Objectives: To document CEI/CEIm ongoing oversight on biomedical research studies. To identify whether or not, a single Committee approval is mostly accepted by all other Committees.

Methods: A survey with nine points questionnaire was conducted, and circulated to 120 different CEI/CEIm in Spain. The following issues were addressed: the explicitness of the CEI/CEIm follow up function in the national regulation; the ongoing oversight conducted in the different CEI/CEIm, and the acceptance of the favorable opinion issued by a CEI/CEIm single and binding on the different biomedical research studies.

Results: 56 Committees fulfilled the survey (44 CEIm and 12 CEI). 66% responded that the national legislation does not establish clearly how to make the follow up of the studies classified as NO clinical trials with medicinal products. 21 committees do not accept the favorable opinion issued by another CEI/CEIm on observational studies and neither biomedical research projects that implies interventions on human beings or that use human biological samples. 25 committees conduct follow up activities for all the studies performed in their site; and 22 committees, do only ongoing oversight of the studies that they have informed favorably. 7 CEIm and 2 CEI do not conduct any follow up activities. The main reason is to have limited resources. Asked by the follow up activities that should be conducted by a CEI/CEIm these were the preferential options: Regular oversight of the studies that they have informed, and circulated to 120 different CEI/CEIm in Spain. The following issues were addressed: the explicitness of the CEI/CEIm follow up function in the national regulation; the ongoing oversight conducted in the different CEI/CEIm, and the acceptance of the favorable opinion issued by a CEI/CEIm single and binding on the different biomedical research studies.

Conclusions: National legislation does not establish clearly how to make the follow up on all the biomedical research studies. There are CEI/CEIm that do not conduct any follow up activities due limited resources.

Not all the CEI/CEIm accept the favorable opinion issued by another CEI/CEIm.

CP08 | Randomized clinical trial to assess a strategy that shortens the time to surgery in patients receiving anti-platelet drugs with a proximal femur fracture (affect study)

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Objectives: Patients with a femur fracture benefit from early surgery. The main objective of this study is to compare the time to surgery since hospital admission between a strategy based on a diagnostic test of platelet functionality and usual clinical practice in patients receiving anti-platelets with proximal femur fracture.

Methods:
Design: Multicenter, open-label, parallel, randomized clinical trial. Trial registration number: NCT03231787.

Patients: It will be included 156 patients of both sexes, over 18 years of age on chronic treatment with anti-platelets who present a proximal fracture of the femur. Patients with multiple fractures, pathological fractures, who receive vitamin K antagonists or new oral anticoagulants and who have some congenital or acquired coagulopathy will be excluded.

Centers: 3 centers, distributed in Spain.

Intervention: Experimental group: The experimental group will undergo surgery within 24-48 hours, as soon as platelet aggregability is correct according to Plateletworks® method. Control group: The control group will undergo surgery according to the usual practice of the center, taking into account the safety time of the anti-platelet drug.

Outcomes: Primary outcome will be time until surgery measured in hours. Secondary outcomes will be platelet functionality, bleeding, medical-surgical complications, perioperative and one-year mortality, quality of life, length of hospital stay, the correlation between the Plateletworks® system and the PFA-100, cost-effectiveness and cost-utility.

Follow-up: Patients will be followed during the hospital admission, at the month of the surgery, at 6 and 12 months.
Results: This clinical trial is running.

Conclusions: We expect that in those patients who receive chronic treatment with anti-platelet, early surgery guided by methods of determination of platelet function, would allow us to individualize the reduction of time to surgery and perform the surgical-anaesthetic procedure with maximum safety.

CP09  |  Overview of erectile dysfunction and premature ejaculation: recommendations for their approach

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Objectives: Given the lack of update prevalence studies of these two pathologies the main objectives are the following:

1. To describe the detection, management, and treatment of Premature Ejaculation (PE) and Erectile Dysfunction (ED), in the office of the UROLOGY SPECIALIST in Spain.
2. To describe the opinions, attitudes, and perceptions of the PATIENT in relation to PE and ED (diagnosis, treatment, and expectations) as well as patient interaction with the urologist.
3. To describe the opinions, attitudes, and perceptions of the GENERAL POPULATION in relation to PE and ED as well as the role of the urologist.
4. To establish recommendations to improve detection and the coping with PE and ED.

Methods: Observational study, based on tridimensional target questionnaires, at National level across the 17 autonomous communities aimed at urologist, patients with erectile dysfunction, with premature ejaculation and general male population.

• A representative sample of 200 urologists will be chosen randomly through the data base of the Spanish Society of Urology (Sociedad Española de Urología).
• A total of 600 patients with ED and 400 with PE will be asked to respond to the patient questionnaire.
• A sample will be selected randomly, stratified by age, representing the male population ranging from 25 to 75 years old (2500 men).
• The participants will respond to the above-described questionnaire. The responses will remain completely anonymous. This stage will be carried out simultaneously to the two previous stages.

Results: The study will be carried out throughout end of 2018 and 2019.

Conclusions: This study will help to establish future recommendations regarding detecting and dealing with ED and PE.

CP10  |  How does clinical trial sponsor manages the information to participants in case of a premature discontinuation?

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Objectives: The main objective is to describe how the clinical trial (CT) sponsor manages the information to participants about the premature discontinuation of the CT when is notified to the Ethics Committee (CEIm).

Methods: A review of the sponsor notifications related to the premature discontinuation clinical trials received at the Bellvitge University Hospital CEIm during two years (2016-2017) was carried out. The notification information collected to achieve the main study objective was the following: (1) the protocol information (sponsor, phase, design, investigational product/medical device, therapeutic area), (2) the trial discontinuation (reasons, patients in the study at the time of the notification, medicine/medical device development program), and (3) patient information (mention in the sponsor notification, instructions to the investigators, information sheet to participants).

Results: Overall, 50 sponsor notifications related to 41 CTs registered as a premature discontinuation were received by the CEIm during the study period. Forty out of 41 CTs evaluated a drug, 35(85%) were sponsored by industry, and the majority were phase II (56%; n = 239 and phase III (39%; n = 16). The main reason for the premature discontinuation was the lack of efficacy (31%; n = 13) and the poor recruitment (30%; n = 9). Among the 17 CTs that had active patients at the moment of the notification, only 7 of them (36%) included aspects of the patient information; the sponsor included a specific document to be given to patients in 3 CT.

Conclusions: The clinical trial sponsor rarely includes the aspects of the patient information in the notification sent to the CEIm. The lack of efficacy and the poor recruitment were the most frequent reasons for the trial discontinuation.
CP11 | EU clinical trial regulation: are the medicines agencies ready to achieve a single opinion?

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Objectives: CT-Regulation EU536/2014 aims to provide a single European assessment for multicenter CTs leading to a single decision, valid for all the concerned member states (MS). Although this procedure is expected to facilitate the conduct of multinational CTs, the current experience with the voluntary harmonization procedure (VHP) points out to some major difficulties for a common assessment.

Methods: We present a regulatory case study, consisting in an EU-approved, non-commercial, multinational, randomized, controlled phase III-CT that evaluates the efficacy and safety of bone marrow-derived stem cells in the treatment of non-union fractures (ORTHOUNION, EudraCT2015-000431-32).

The same investigators/sponsor previously had obtained national approvals at the same MS (Spain, France, Germany, Italy) for 2 other CT, using the same IMP, produced by the same manufacturing facilities.

A VHP procedure was selected in all concerned MS, using VHP-plus (with parallel Ethics Committees evaluations) in Germany and Spain.

Results: After initial submission (09/01/2017), a list of 25 grounds for non-acceptance was received (20/02/2017):
- Quality: clarifications on controls/reagents, additional validation results;
- Clinical: clarifications on trial population and safety information;
- Statistics: details on sample size calculation, non-inferiority margin, endpoints.

After responses were sent (27/02/2017), a divergent decision was received (22/03/2017): France and Spain considered the CT-application approvable, subject to the submission of additional quality documents, while Germany and Italy considered these same issues unsolved via VHP. None of the issues fell within the scope allowed by the EU Regulation 536/2014 as grounds for disagreement.

VHP approval was received (19/04/2017), followed by national approvals for France (18/05/2017) and Spain (25/05/2017).

Re-submissions were presented nationally to Italy and Germany with additional quality documents. Approvals were obtained on 28/02/2018 and in May 2018, respectively.

Conclusions: The VHP divergent opinion, based on grounds not recognized by the EU CT-Regulation as reasons for disagreement between Agencies, resulted in an unnecessary delay of over 12 months and added a pointless and time-consuming bureaucratic burden. It is necessary to ensure that discrepancies would not result in a full refusal once the new CT regulation comes into application.

CP12 | Effect of moderate ethanol consumption on the steroid profile and ethanol biomarkers (dose effect study)

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Objectives: To determine the correlation between ethanol direct biomarkers (EtG) and Ethyl sulfate (EtS) in urinary concentrations and changes in the T/E (Testosterone/Epitestosterone) ratios and other parameters of the steroid profile after intake of ethanol.

Methods: Twelve healthy male volunteers participated in a randomized, cross-over balanced with placebo clinical trial. Subjects were distributed in two different cohorts. One cohort (n = 6) received 18 and 30 g of ethanol (pharmaceutical grade) and another cohort (n = 6) received 24 and 42 g of ethanol respectively. Study variables include urine samples for EtG an EtS and the steroid profile parameters testosterone (T), epitestosterone (E), androsterone (A), ethicoxol (Etio) 3a,5a-androstanediol (5aAdiol), 3a,5b-androstanediol (5bAdiol) were determined following standard analytical procedures by GC/MS.

Results: Concentrations of both EtG an EtS in urine peak at 4-6 h after alcohol consumption are detectable up to 12 hours. Changes induced in T/E ratio at the doses tested are mainly observed in the period from 0 to 4 h after alcohol consumption. Mean changes may vary from 5% in the period 0-2 h to 170% in the 2-4 h period. EtG concentrations do not correlate well with T/E for that precise period maximum T/E variations (0-4 h). The parameter T100/A (Testosterone multiplied by 100/Androsterone) fits better with changes in Etg than the T/E ratio. The ratios A/Et or 5aAdiol/5bAdiol were not affected.

Conclusions: EtG concentrations in urine had a delayed profile. While EtG concentrations were quite low in the period 0-2 h (below 20 µg/mL), T/E values had already varied significantly. However, when EtG concentrations
were maximal (around 60-70 µg/mL). T/E values had already begun to decline or had already returned to normal. In conclusion, EtG and EtS are not good markers explaining or justifying T/E variations. Even so, a linear correlation has been found between the alcohol dose and the T/E variation.

Acknowledgements: Grant from Instituto Carlos III (J. Mateus is a Rio Hortega CM17/00024).

CP14 | Experimental administration of two doses of alcohol simulating a binge drinking episode in young adults

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Objectives: Binge drinking (BD) it has become trendy among adolescents and young adults. It is defined as a pattern of drinking that reach blood alcohol concentration (BAC) to 80 mg/dL in a short period of time (2 hours), that typically occurs after 4 drinks for women and 5 drinks for men. The aim of this study was to evaluate BAC and acute effects after the administration of two different high doses of alcohol simulating a binge drinking episode under experimental conditions.

Methods: Fifteen healthy male volunteers, with previous BD behavior participated in one experimental session. They received an oral dose of 70 grams (n = 11) or 100 grams of alcohol (n = 4), mixed with zero orange soda without bubbles (Trina®) distributed in 6 glasses (total volume 900 mL) over a 2-hour period (20 minutes for glass). Low dose were allocated before high dose for safety reasons. The trial was single-blind, non-randomized and non-controlled. Study variables included vital signs, subjective effects and BAC measured along 12 hours.

Results: Preliminary results show that both doses produced the prototypical alcohol effects (VAS drunkenness, BAES stimulant and sedative effects). With regard to BAC, higher Cmax values were achieved after 100 grams. BAC remained >80 mg/dL along 3 and 4 hours after 70 and 100 g administration, respectively. There were no serious adverse events.

Conclusions: Total oral doses of 70 and 100 grams of alcohol, administrated in 2 hours period achieving BAC>80 mg/dL, in subjects with previous BD behavior are well tolerated. This model can be used to assess experimentally acute effects of alcohol related to binge drinking pattern.

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CP13 | Cart gene therapy trial in the academic settings

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Objectives: The first administration in humans (FIH) of an investigational medicinal product (IMP), either conventional or advanced (ATMP) presents a challenge. It is classified as a high risk study because of the limited information available on the IMP, rigorous data source verification needs to be performed in these trials.

CART19-BE01 is a FIH study with a CART gene therapy addressed to patients with refractory leukaemia, developed and manufactured in an academic setting. The objective is to share our experience in the implementation, development and conduction of a FIH clinical trial (CT) sponsored by an academic institution highlighting key processes, lessons learned and providing recommendations to allow other CT Units in the conduction of similar CTs.

Methods: A review of the timing and major milestones of the trial was performed. Time needed to set up the CT was calculated in terms of: CT documentation package (protocol/IMPD/IB) writing, green lighting and recruitment. Median follow-up days of current participants were calculated.

Results: CT documentation package drawing up took 11 months, obtaining the final authorization (Competent Authority + Ethics) took 140 days and the first patient was included 1 month later. To date, a total of 26 patients have been recruited, 18 patients have been infused with CAR T-cells and the median of follow-up is 126 days. More than 100 professionals are involved in this CT.

Conclusions: Public institutions and governments should support and provide resources to cover ATMP initiatives addressed to fulfil unmet medical needs. FIH-ATMP CTs require specialized units and long-term involvement of qualified personnel is essential. Standards are very high and CTUs resources are usually limited and costs are therefore assumed by units/institutions. CART19BE01 requires a multidisciplinary, close collaboration, transparency and specific know-how but it is feasible within the adequate environment.
ABSTRACTS

CP15 | New psychoactive substances: observational study of the acute effects of mephedrone and methylone

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Objectives: In recent years the drugs of abuse scene has been changed with the introduction of new-novel psychoactive substances (NPS), more than six hundred NPS have been found in the market. Most relevant NPS are synthetic cannabinoids and cathinones. In this study we describe the acute pharmacological effects of methylene and mephedrone in humans.

Methods: Two naturalistic-observational studies in a non-laboratory setting. In the first study, ten healthy recreational drug users (seven males and three females), self-administered a single dose of mephedrone by oral route (n = 5; mean single dose 150 mg, range 100 to 200 mg) or intranasal route (n = 5; mean single dose 70 mg, range 50 to 100 mg). In the second study, eight healthy recreational drug users (five males and three females), self-administered a single dose of methylone by oral route (200 mg, range 100-300 mg). Study variables (0-4 h) included vital signs (systolic and diastolic blood pressure, heart rate and temperature, and subjective effects (visual analogue scales).

Results: As expected, mephedrone produce a significant increase in blood pressure and heart rate and induced positive subjective effects (stimulant-like effects, euphoria, and well-being). Methylene induced similar effects, but during more time than methylene. There were no serious adverse events. The results observed in the naturalistic-observational setting for mephedrone and methylene were similar to those found in a human pharmacology unit when administering amphetamines, MDMA or mephedrone in controlled conditions.

Conclusions: New NPS produce similar effects of classical substances as amphetamine and MDMA, showing a high abuse liability properties that could explain its illegal use in young.

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CP16 | Influence of enos gene on cardiovascular risk in erectile dysfunction patients

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Objectives: To analyze the influence of eNOS gene variants on effectiveness of a referral pathway for patients with Cardiovascular Risk (CVR), where Erectile Dysfunction (ED) is diagnosed as sentinel symptom and derived to Andrology Unit.

Methods: An observational study is performed on 80 patients with CVR and ED. The subjects were patients from Cardiovascular Unit and referred to Andrology Unit for ED diagnosis and treatment. Derived patients are followed for a period of 6 months upon treatment. Patients demographic, cardiovascular co-morbidities and pharmacological data were registered. The ED was assessed with the International Index of Erectile Function (IIEF) and its sub-domain (IIEF-EF), the sexual quality of life by mSLQQ test and anxiety/depression by HAD-A/HAD-D tests. Genetic analysis of T786C, G894T polymorphisms of eNOS gene were made by RT-PCR. The project was approved by Ethical Committee and analysed by R.3.2.0.

Results: Our population (preliminary group of 11 males, 61.3 ± 6.3 years old, 100% Caucasian) have suffered at least one cardiovascular accident and presented ED (IIEF 34.0 ± 11.7 and IIEF-EF 8.6 ± 6.4 scores and low quality of sexual life mSLQQ -15.8 ± 6.1 scores). Regular laboratory test were in normal ranges, except for a lower HDL (40.8 ± 9.2 mg/dl). Acetylsalicylic acid or statins were prescribed in more than 80% of patients. Our population did not show anxiety (3.8 ± 2.6) or depression (1.9 ± 2.3). Patients were heterozygote (50%) or homozygote variant (50%) for T786C polymorphism; while 86% were wild type and 14% heterozygotes, for G894T polymorphism.

Conclusions: ED was a sentinel symptom for CVR under diagnosed in our population that has a very poor sexual quality of life. This seems not affecting psychological profile being also under treated. One of the most clinically relevant polymorphisms in the promoter region (T786C) is
Objective: To evaluate bioavailability pharmacokinetic parameters of omeprazole in patients undergoing Roux-en-Y gastric surgery (RYGS).

Methods: Multiple-dose, open-label, cross-over bioavailability study in patients undergoing RYGS and control subjects (body weight-paired to +6 month post-surgery patients). Healthy overweight/obese patients 18-60 years old were included. The assessment was performed once in Control patients and three times in Case patients (before, +1 and +6 months after surgery). In each visit, after overnight fasting, the subjects received a single oral dose of omeprazole 20 mg. Venous blood samples were obtained at baseline and 1, 2, 2.5, 3, 3.5, 4, 5, 7, 9 and 12 hours after omeprazole intake. Pre- and post-surgery variables were compared using paired ANOVA or Wilcoxon tests, and control vs. cases using ANOVA or Mann-Whitney. Given the post-surgery change in body weight, parameters were corrected by dose (mg/body weight (kg)). The analysis was performed using WinNonlin and SPSS.

Results: 34 subjects completed (17 cases and 17 control) the study (92.9% female). Omeprazole Cmax was significantly reduced at +1 and +6 m after surgery (749.3 ± 377.0 vs 461.9 ± 365.7 ng/mL, P = 0.001; 749.3 ± 377.0 vs 486.1 ± 348.5 ng/mL, P = 0.003). There was not statistically significant difference in Cmax between cases at +6 m and control group (486.1 ± 348.5 vs 515.9 ± 386.2 ng/mL; P = 0.819). After correcting by the dose (mg)/patient's body weight, both Cmax and AUClast showed significant decreasing at +1 and +6 m after surgery (Cmax: 65.5 (34.0-158.8) vs 56.5 (33.1-135.4) ng/mL/dose (mg)/weight (kg); P = 0.001 respectively, vs 134.6 (100.2-226.2) ng/mL/dose (mg)/weight (kg) at baseline; AUC: 123.2 (47.9-409.7) and 142.2 (40.7-367.2) h*ng/mL/dose (mg)/weight (kg)) at baseline; then showed different Cmax and AUC at +6 m post-surgery showed lower values than the control group (69.5 (34.0-158.8) vs 76.6 (36.4-110.6) h*ng/mL/dose (mg)/weight (kg); P = 0.001), and also AUC (142.2 (40.7-367.2) h*ng/mL/dose (mg)/weight (kg)) vs 142.4 (66.1-365.4); P = 0.029).

Conclusions: Omeprazole absorption is impaired at +1 m and +6 m after RYGS. It is necessary to determine the impact in the treatment of this patients.

Objective: To analyze the influence of CYP2D6 ultra-rapid metabolic phenotype in patients with non-cancer chronic pain and prescription opioid dependence (POD).

Methods: Observational study following up an individualized deprescription plan during 6 months with tapering of morphine equivalent daily doses (MEDD) and rotation to buprenorphine and tramadol (n = 120). Pain intensity and relief, quality of life, opiate withdrawal syndrome, global activity and adverse events (AEs) information was collected. Patients were classified as responders to deprescription if a reduction of at least 30% MEDD was achieved, without dependence behavior. Genetic analysis of CYP2D6 *2, *3, *4, *6, *10, *17, *29, *35, *41 (n = 67) was performed by real-time PCR, as well as number of copies, grouping the subjects as poor (PM), extensive (EM) or ultra-rapid (UM) metabolizers. The project was approved by Ethical Committee and analyzed by R 3.2.0.

Results: Study population (53 ± 13 years old, 60% female) showed a moderate pain intensity and relief, with 71% of responders to deprescription. A total of 310 AEs were registered, with a median of 7 (4-9) per patient. Dry mouth (66%) and sleep disruption (53%) were the most frequent. Metabolic phenotypes frequencies were 6% PM, 84% EM and 10% UM without any influence on clinical or drug variables. Different phenotypes frequency (PM, EM and UM) were found in AEs: headache (50, 33 and 100%), dry mouth (0, 63 and 100%) and depression (0.46 and 83%) distribution.

Conclusions: UM-CYP2D6 phenotype chronic pain patients with POD, showed a different opioid security profile especially of neurology or psychiatric AEs.
CP19 | Application of pharmacokinetic and pharmacodynamic principles (AUC/MIC) to individualize treatment with vancomycin in neonatal population

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Objectives: Vancomycin monitoring is based on determining trough levels (Cmin) before administering next dose; however, the bactericidal effect of in-vitro vancomycin and its clinical efficacy has been related to the pharmacodynamic parameter $AUC_{0-24}/MIC \geq 400\text{mcg.h/mL}$. The aim was to analyze the $AUC_{0-24}/MIC$ availability in neonatal intensive care unit (NICU) monitored patients and to evaluate, if we had reached the therapeutic objective proposed in literature.

Methods: A sample of newborn ($n = 76$) with stable values for Cmin and Cmax was obtained. Pharmacokinetic parameters were calculated. When MIC for gram-positive microorganisms was available in the antibiogram, $AUC_{0-24}/MIC$ ratio was calculated. The study was approved by an Ethics Committee.

Results: Diagnoses in the patient cohort (46 boys and 30 girls, median gestational-age 29 weeks, median postmenstrual-age 30 weeks) were as follows: late sepsis (58%), early sepsis (22%), bacteremia (5%), septic shock (5%) and others (10%). Susceptible organisms (Coagulase-negative staphylococci (85%), Enterococci (7%), S. aureus (4%) and Streptococcus (4%)) were isolated in 45 patients. Median treatment lasted 7 days. With initial vancomycin dosing according to Neofax recommendations ($11.9 \pm 10.4\text{mg/kg/dose}$), 56% achieved the goal Cmin ($5-15\text{mg/dl}$) and 32% had suboptimal Cmin (<5 mg/dl). Gestational-age had a significant effect on trough levels achieved. In 30 patients $AUC_{0-24}/MIC$ was calculated and only 10% exceeded 400 mcg.h/mL. After dose adjustment, 39 patients were monitored for a second time, and therapeutic Cmin was achieved in 79%; however, only six out of 22 patients (27%) achieved an $AUC_{0-24}/MIC \geq 400\text{mcg.h/mL}$. No significant changes in renal function occurred.

Conclusions: Vancomycin dosing strategies in neonates, such as those found in Neofax, are insufficient to achieve therapeutic concentrations of vancomycin in neonates. Furthermore, therapeutic trough levels do not always correlate with $AUC/MIC \geq 400\text{mcg.h/mL}$, however the role of $AUC_{0-24}/MIC$ in neonatal population is not well-established. Therefore, studies with larger number of paediatric patients are needed to assess the clinical efficacy of this parameter.

CP20 | Role of azathioprine dose's adjustment based on genotyping of Tiopurin methyltransferase (TPMT) on toxicity control in patients with digestive's pathology

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Objectives: Presence of alleles *2, *3A, *3B, and *3C, in the genotyping of the TPMT gene is associated with a decreased activity of the enzyme that metabolizes azathioprine. This fact facilitates the appearance of toxicity. We evaluate whether adjusting the dose of azathioprine based on genotyping reduces the risk of hematological toxicity in our population with digestive pathology.

Methods: Retrospective study on 166 inflammatory bowel disease and autoimmune hepatitis’s patients, who were genotyped for TPMT between 2011 and 2017 at the HUMV. Samples were genotyped by Applied Biosystems Genotyping Assays with TaqMan probes. We used Xi square for statistical analysis.

Results: A 10.8% of our population presented at least one mutated allele. The genetic variants found were: *1/*3A (66.7%), *1/*2 (16.7%), *1/*3C (11.1%) and *3A/*3A (5.6%). This adjusts to expected distribution in Caucasian population.

Of 166 patients genotyped, only 106 received treatment with azathioprine; Of them, 97 patients were Wild type and 9 presented mutated alleles. Wild type patients, received azathioprine at an initial dose of 2 mg/kg/day, and it was increased according to clinical criteria. Hematological toxicity was found in 34% of cases (The most significant toxicities were anemia (21.6%), leukopenia (3.1%), thrombocytopenia (5.2%)).

Patients treated and with mutated alleles were heterozygotes and received 50% of the usual dose of Azathioprine. Hematological toxicity was found in 33% of cases (The most significant toxicities were anemia and leukopenia (both 11.1%))

No significant difference was found in toxicity between both groups ($P = 0.63$).

Conclusions: The presence of alleles *2, *3A, *3B, and *3C acts as a barrier to initiate treatment with azathioprine, as shown by the fact that only 50% of patients in this situation were treated. However, azathioprine's dose adjustment by TPMT genotyping, following the recommendations established, show that there are no differences in toxicity between patients with or without mutations in our population.
CP21 | Metabolizer phenotype and pharmacological safety in the treatment of autistic spectrum disorder

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Objectives: Evaluation of Metabolize phenotype influence in the Adverse Drug Reaction (ADR) of Autism Spectrum Disorder (ASD) population.

Methods: In a two-year ambispective observational study in people diagnosed with ASD (n = 120) by DSM5 criteria. Their clinical, pharmacological history was recorded (comorbidities, % prescription, average dose). The following were selected: (a) Three suspicions ADR due to its high prevalence (obesity, extrapyramidal and acute urine retention); (b) Potential drug interactions in each case; (c) Prescribed dose according to recommended range, higher or lower. In addition, was evaluated the influence of the CYP2D6 metabolizer, that is involved in the metabolism of the main drugs used in the treatment of this population group, this profile was evaluated: poor (PM), extensive (EM) and ultrafast (UM) at the dose of drug prescribed. Finally, relationships between the different variables were established through a multinomial logistic regression. The study was approved by the centers CEIC and analyzed with R 3.2.0.

Results: Preliminary analyzes of a sample of people with ASD with a mean of 28 ± 7 years, 100% males and a median of 4 prescribed medications, around 85-90% received the therapeutic dose within the range recommended in the technical sheets. A total of 20 suspected ADR were analyzed, where a significantly lower association was found between the prescription of doses above the range and CYP2D6 inhibitory drugs. As well as a significantly higher association between the prescription in the range of recommended doses that was greater between CYP2D6 EM and UM metabolizer profiles, in comparison with the PM phenotype.

Conclusions: The results showed that the CYP2D6 metabolizer phenotype influences the prescribed dose in the ASD population, of which an ADR is suspected. The possibility of attaching a simple genetic diagnosis of these enzymes, would be a greatly help in the clinical and pharmacological work of the professionals.

CP22 | Effectiveness and analgesic security regarding metabolic profile in non-oncologic chronic pain patients treated with oxycodone

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Objectives: To know the influence of genotypic and phenotypic factors related with cytochrome P450 (CYP2D6 y CYP3A4) in the analgesic response of oxycodone-naloxone (OXN) in patients with non-oncologic chronic pain.

Methods: Observational study of patients with DCNO, treated with oxycodone (n = 108), comparing with a general population treated with opioids (n = 754) and with another control population which doesn't receive OXN (n = 216) analyzing their clinical records and phenotype, assessing their pain and intensity of pain (EVA, visual analogical scale), the relieve (EVA), life quality (EuroQol) and adverse events (EA). Saliva samples were taken. Later a statistical analysis was performed in order to asses if metabolic profile (CYP2D6 poor, extensive, ultra-fast) and genetic variants of CYP3A4 affects the analgesic effectiveness and security.

Results: Group treated with OXN (65 ± 14 years, 79% female, pain intensity 63 ± 27 mm, relief 40 ± 30 mm y life quality 46 ± 23 mm) had a greater relief intensity when their metabolism increases its speed, no changes were found related with security (5.8 AE/patient) comparing with control groups. The patients % regarding the metabolic profile was: poor 6.5%, extensive 87% and ultra-fast 6.5%. No significant differences were found regarding metabolic profile nor CYP3A4.

Conclusions: Phenotypic metabolizer of CYP2D6 affects in the analgesic of OXN, being better when the metabolism is faster, although it doesn't affect its security.

CP23 | Evaluation of polymorphisms and influence of them on the pharmacokinetics of imatinib in healthy volunteers: pilot study

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Objectives: To examine whether genetic variations and/or altered expression of ABCB1 gene and cytochrome P450...
isozyme genes, may influence the pharmacokinetics (PK) of imatinib in healthy volunteers in the context of two bioequivalent studies.

**Methods:** This is a pharmacogenetic study pilot in 26 healthy volunteers who previously participated in two bioequivalence clinical trials with oral imatinib 400 mg. Thus, previously in the bioequivalence studies volunteers were randomized to receive both imatinib formulations (Reference/Test), followed by washout time. Plasma concentrations were analyzed in bioanalytical laboratories by validated HPLC-MS/MS. For the pharmacogenetic study we were included volunteers who previously performed a bioequivalence trial of imatinib at their respective centers (phase I clinical trial Units: Units of Alicante and La Paz University Hospitals). They granted their express informed consent for the extraction of blood samples and the subsequent DNA extraction. Genotyping was performed in the laboratory of the Clinical Pharmacology Department of La Princesa University Hospital. Gene polymorphisms analyzed, in real-time PCR, were CYP isoenzymes (CYP3A4 and CYP3A5, CYP2C9, CYP2C19, CYP2D6, CYP2B6) and of ABCB1. Metabolizer status was classified according Gaedigk’s criteria. For statistical analyses R 3.2.0 and GraphPad Prism 5 were used.

**Results:** Volunteers (24 ± 3 years old; 69% male; 100% Caucasian, BMI 23 ± 3 kg/m²) presented regular imatinib PK (concentration 39.1 ± 27.2 ng/mL, AUC 32 868 ± 10 713 ng*h/mL, Cmax 2.074 ± 604.4 ng/mL) without differences between formulations. Results showed the following: lower concentration and elimination half-life (t1/2) in CYP2B6 heterozygotes and a lower Cmax and AUC in CYP2D6 extensive metabolizers.

**Conclusions:** Findings would support the use of CYP2B6 and CYP2D6 phenotype as markers to arise PK parameters in imatinib administration. We don’t detect differences when analyzed by age, sex, weight and BMI.

**CP24 | Association between therapeutic drug monitoring reports and dispensation of antiepileptic and antibiotic drugs in a tertiary hospital in the period 2009-2017**

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**Objectives:** To describe the evolution and association between the number of therapeutic drug monitoring reports (TDMR) generated by the Clinical Pharmacology Service in a tertiary hospital and the dispensations (units) by the Hospital Pharmacy Service (DHPS) of both antibiotics (gentamicin, tobramycin, amikacin and vancomycin) and antiepileptic drugs (carbamazepine, phenytoin, phenobarbital and valproate) in the period 2009-2017.

**Methods:** The association was analyzed through Pearson correlation coefficient (r) and linear regression.

**Results:** Vancomycin was the antibiotic with both the highest number of TDMR’s (701 ± 141) and DHPS’s (19634 ± 3037) (r = 0.886; P = 0.001). The average DHPS’s not associated to TDMR’s was 6203, and for each TDMR 19 DHPS’s were carried out. Tobramycin was the antibiotic with both the lowest number of TDMR’s (99 ± 38) and DHPS’s (3054 ± 1003) (r = 0.831; P = 0.006). The average DHPS’s not associated to TDMR’s was 871, and for each TDMR 22 DHPS’s were carried out. Valproate was the antiepileptic drug with both the highest number of TDMR’s (754 ± 65) and DHPS’s (10708 ± 3009) (r = 0.749; P = 0.02). The regression slope was negative, which could be explained by a decrease in DHPS’s while TDMR’s increased slightly over time. Phenytoin had an average TDMR’s of 131 ± 55 and DHPS’s of 5232 ± 2892 (r = 0.817; P = 0.007). In this case, all of the DHPS’s were associated to TDMR’s, and for each TDMR 43 DHPS’s were carried out. In addition, both TDMR’s and DHPS’s decreased notoriously over time.

**Conclusions:** Vancomycin displayed the highest correlation between TDMR and DHPS followed by tobramycin. Over time, valproate showed an increase in the number of TDMR in relation to DHPS, while phenytoin suffered a pronounced decrease in both DHPS and TDMR.

**SECTION: C. PHARMACOVIGILANCE, SAFETY AND QUALITY**

**CP25 | Detection of adverse reactions associated with opioid treatment in the emergency department of H.U. LA Princesa**

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**Objectives:** The occurrence of adverse reactions (AR) is an important cause of poor adherence to opioid treatment. Identify the number of AR associated with opioid treatment that are consulted in the Emergency Department (ED) can be useful to implement preventive actions to reduce the frequency of adverse effects and thus improve both adherence to treatment and the control of pain. The main objective of
the study is to implement a proactive pharmacovigilance system for the detection of AR in patients with opioid therapy who come to the ED to determine which AR are the most frequent and identify demographic and/or clinical factors that confer an increased risk of suffering an adverse reaction.

Methods: An observational, retrospective, descriptive and cross-sectional study was conducted to detect possible AR to opioids through the review of medical records of patients who arrived at the ED from January to June 2016 and in whose history some “Key Word” appeared. To establish the causality relationship between the drug and the adverse reaction, we applied the causality algorithm of the Spanish Pharmacovigilance System.

Results: A total of 447 adverse reactions were recorded in 291 patients. Of the 49532 patients who went to the ED, 3281 (6.62%) had opioids in their treatment and 8.87% of these (291 patients) had some adverse reaction. Of the 447 adverse reactions, 73.15% appeared in women; 75.84% in ≥65 years and 74.50% in polymedications. The most frequent ARs were gastrointestinal (53.02%) and central nervous system (21.92%). Tramadol is the most frequently identified opioid appearing in 51% of events.

Conclusions: Adverse reactions to opioids are an important cause of poor therapeutic compliance. In many cases they are preventable, and their recognition and prophylaxis must be improved. More pharmacovigilance studies are needed in daily clinical practice to finally optimize the therapeutic adherence and thus achieve better pain control.

Objectives: To describe main characteristics of patient suspected adverse drug reactions (ADRs) reports to the Catalan Centre of Pharmacovigilance (PhVCC) through www.notificaRAM.es during the first four years since its implementation.

Methods: Patient reports of suspected ADRs received in the PhVCC from 15/01/2013 to 15/01/2017 were included. We analyzed patient’s demographic characteristics, types of ADRs, their seriousness, suspect drugs, previous ADRs knowledge, lag between the ADR occurrence and reporting, and information provided in free text section.

Results: During the study period, the PhVCC received 4551 spontaneous reports of ADRs; 190 of them (4.2%) from patients, and increased from 19 the first year to 77 the last. The mean age of patients was 39 years, mostly women (63.7%). Cases described 383 ADRs, which 28.6% were unknown or poorly known and 52.1% serious. The most frequently reported ADRs were gastrointestinal (74; 19.3%), neurological (73; 19.1%) and cutaneous (47; 12.3%). The total number of suspect drugs was 213. The most frequent therapeutic groups were nervous system (40; 18.8%), anti-infective (36; 16.9%) and respiratory system drugs (28; 13.1%), highlighting sex hormones and vaccines as uppermost subgroups (both 17; 8%). Nineteen (8.9%) suspected drugs were under additional monitoring (DUAM) and 27 (12.7%) were over the counter. The mean lag from ADRs occurrence to report was 82.8 days, most done in less than a month (108; 56.8%). Nearly 25% (46) of reports which had free text provided additional useful data for ADRs evaluation: about temporal sequence (27), description of symptoms (20) and psychosocial impact (19).

Conclusions: Patient reports have increased since 2013. More than a half were serious; one-third described unknown ADRs, and one-tenth concerned DUAM. Mostly were reported in less than a month after ADRs occurrence. Free text section provided useful information and added patient’s point of view. So, their participation should be actively promoted to enrich the pharmacovigilance system.

CP27 | A case of repeated neutropenia after vancomycin, teicoplanin and dalbavancin

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Objectives: Dalbavancin is a novel semisynthetic glycopeptide antibiotic that has the same mechanism of action as vancomycin although it is effective in vancomycin-resistant Enterococcus and Staphylococcus with intermediate sensitivity to glycopeptides. Neutropenia induced by glycopeptides is an uncommon but potentially serious and life-threatening undesirable effect. There is not data available on neutropenia caused by cross-reactivity between dalbavancin with other glycopeptides.

We describe, for the first time, a case of recurrent neutropenia induced by vancomycin and subsequent related to teicoplanin and dalbavancin.

Methods: A 53-year-old male was admitted to our hospital for the treatment of persistent bacteremia caused by Enterococcus faecium. In last year, he was treated with vancomycin in four episodes, presenting neutropenia in last three ones. In the present episode, he received teicoplanin
and developed a new episode of neutropenia 21 days after treatment initiation with a white blood cell (WBC) count of 1.8x10^3 mm^3 and absolute neutrophil count (ANC) of 0.7x10^3 mm^3. Neutropenia resolved in 2 days following withdrawn of the drug and two doses of granulocyte-colony stimulating factor (G-CSF). Teicoplanin was replaced by the structurally related compound dalbavancin. Three days after, another episode of neutropenia occurred (WBC count of 1.6x10^3 mm^3 and ANC of 0.16x10^3 mm^3). Dalbavancin was discontinued and G-CSF was administrated. WBC count and ANC rapidly returned to normal. Since discharge, patient's ANC count has remained within the normal range.

**Results:** Neutropenia probably related to dalbavancin was resolved after drug discontinuation and G-CSF therapy, similarly to other glycopeptides.

**Conclusions:** Clinicians should be aware that neutropenia could be induced between old glycopeptides including the new dalbavancin probably by potential cross-reactivity.

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**CP28 | Case-control study on lactic acidosis associated with metformin in diabetic patients with moderate to severe chronic kidney disease: ALIMAR-C2 protocol**

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**Objectives:** To assess the association between metformin use and lactic acidosis (LA) in patients with type 2 diabetes mellitus (2DM) and moderate-severe chronic kidney disease (CKD).

**Methods:** ALIMAR-C2 is a case-control study using electronic healthcare databases from a group of hospitals and their corresponding primary healthcare areas. LA cases will be identified from hospitals and matched by gender, age, and CKD stage with 10 community controls. Cases will be patients aged ≥18 years with 2DM diagnosed before the index day (ID; the day of admission) and moderate-severe CKD (glomerular filtration rate 15-60 mL/min) during the prior 2-year period who are admitted with LA (pH <7.35 and lactic acid >5 mM/L). Patients with diagnoses of type 1 diabetes mellitus, HIV infection, or transplant before the ID, neoplasms less than 5 years before the ID, discharge diagnosis of diabetic ketoacidosis, no assignation to the reference area of the hospital, or no information registered in the primary healthcare system during the year before the ID will be excluded.

**Results:** ALIMAR-C2 study obtained a grant from the Instituto de Salud Carlos III in 2015 (PI15/00764). It was approved by the Clinical Research Ethics Committees of the participating centers, classified by the Agencia Española de Medicamentos y Productos Sanitarios as a post-authorization study (PAS), and registered in the European register of PASs (EU PAS13969) receiving the ENCePP seal. A pilot phase was conducted in 2017 to test the feasibility in all centers initially invited to join the project. Eight hospitals with their corresponding primary healthcare areas, with an overall follow-up about 18 million patient-years, met the requirements to participate in the study that is currently ongoing. Preliminary results are expected by the end of 2018.

**Conclusions:** Results from ALIMAR-C2 study will provide useful information regarding the safety of metformin in patients with 2DM and CKD.

**CP29 | Unacceptable toxicity: Adverse drug reactions identified from a register of patients treated with outpatient hospital medicines**

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**Objectives:** In Catalonia patients treated with some outpatient hospital medicines (OHMs) have been recorded on a register since 2014. The aim was to analyze how often unacceptable toxicity led to OHMs withdrawal as well as the adverse drug reactions (ADRs) and medicines more often involved.

**Methods:** A retrospective observational study was carried out on all registered cases in which OHMs were withdrawn due to unacceptable toxicity in our hospital from 2014 to 2017. Information on patients’ demographic and clinical characteristics, OHMs and concomitant treatments, and ADRs that led to OHMs’ withdrawal was collected from the register and electronic medical and prescription records. Moreover, information on whether OHMs had a special monitoring and whether ADRs were included in the OHMs’ risk management plans was obtained from the EMA website.
CP30  |  Antituberculosis drug-induced liver injury (ATDILI): assessment of drug causality and pathogenesis with lymphocyte transformation test (LTT) and pharmacogenetics (PHGX)

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**Objectives:** First-line drugs for Tuberculosis are isoniazid (H), rifampicin(R) pyrazinamide(Z), and/or Ethambutol(E). The incidence of drug-induced liver injury during this four drugs regimen has been variably reported as 2-30%. Its pathogenesis is poorly understood.

Our objective was to elucidate the pathogenesis of ATDILI and to detect biomarkers that could predict liver injury.

**Methods:** We herein report two cases of ATDILI.
CASE 1: received R, H, Z, and E 9 days. On day 9 he showed hepatocellular injury and prolonged prothrombin time. Cessation of treatment led to normalization of enzyme levels.
CASE 2: was admitted to our hospital presenting jaundice. She was on the 35 day of R, H, Z and E treatment. Laboratory tests showed hepatic insufficiency. After treatment discontinuation laboratory values returned to normal.

In both patients alternative causes were excluded and RUCAM algorithm was applied.
LTT has been proposed to determine if a drug is the causal agent of immune-mediated ATDILI. It was performed in both patients for H, R, Z, and E.

In addition, a PhGx test for N-acetyltransferase (NAT2) which acetylates H and is involved in metabolic ATDILI, was performed. A total of five polymorphisms (rs1041983, rs1801280, rs1799929, rs1799930 and rs1208) were genotyped using amplification by PCR.

**Results:** H, R, Z, E were classified as “highly probable”(10 points) by RUCAM algorithm in both patients.
Rest of medication was excluded due to lower algorithm scores or dates of administration and rise of liver enzymes.
In CASE 1, LTT was negative, however, PhGx test revealed two slow NAT2 alleles (*5/*6).
LTT in CASE 2 was positive for H and Z and presented two wild type NAT2 alleles (*4/*4).

**Conclusions:** In light of these results we concluded ATDILI can be both genetically determined, or immune mediated. These tests help us to explain the pathogenesis of ATDILI, to establish its culprit agent and to predict individual risk of slow NAT2 acetylators allowing us to make more precise recommendations.

CP31  |  Outcomes of pregnancies exposed to biological drugs

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**Objectives:** Although studies have shown no evidence of teratogenicity with some biological drugs (BD), the available data is too limited to exclude adverse effects on the fetus. The aim of this study was to evaluate the outcomes of pregnancies exposed to BD.

**Methods:** A retrospective observational study of enquiries received at the Teratogen Information Centre of VHUH between January 2000 and December 2017 about pregnancies exposed to BD was performed. Inclusion criteria were enquiries about exposure of the mother or the father to monoclonal antibodies or fusion proteins. Exclusion criteria were enquiries about vaccines, recombinant hormones, hematological derivatives and receptor antagonists, and those without information to identify patient’s medical records.

**Results:** Thirty-nine enquiries were included. In 36 (92.3%) the exposed person was the woman and in 3 (7.7%), the man. They were exposed to 13 different drugs, being the most frequent: adalimumab (11; 26.8%),
etanercept (10; 24.4%) and infliximab (6; 14.6%). Their main indications were Rheumatoid Arthritis (15; 37.5%) and Crohn Disease (11; 27.5%). The results of these pregnancies were 28 (71.8%) live-born children, 2 of them (7.14%) with malformations (abnormalities due to oligohydramnios and congenital heart defects, 1 exposed to trastuzumab/pertuzumab and 1 to trastuzumab-emtansine) and 2 other (7.14%) live-born children presented recovered post-natal respiratory distress. There were 10 (25.5%) abortions: 6 elective terminations [1 because of fetal malformation and 5 due to exposure to a teratogenic drug (4 of them also exposed to methotrexate)], 3 spontaneous abortions and 1 anembryonic pregnancy. There was 1 unknown outcome.

Conclusions: Our findings showed a high percentage of live-born children with no malformations. Nevertheless, there was also a high percentage of adverse outcomes, particularly in those exposed to trastuzumab-emtansine, trastuzumab/pertuzumab and other teratogenic drugs. These results provide data on the safety of some BD during pregnancy, however, further studies are needed to assess their potential risk.

**CP32 | An effective management of adverse events reporting to ensure patient safety: main pharmacovigilance problems detected during monitoring activities in independent multicenter clinical trials**

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Objectives: SCReN is a network providing pharmacovigilance (PV) and monitoring support to conduct independent multicenter clinical trials. Management and reporting of adverse events (AE) and other safety occurrences are critical for ensuring patients safety. Study monitors are responsible of safety training to investigators. Thus, a good understanding of safety procedures is key to guarantee appropriate adverse events management and therefore to ensure an adequate safety assessment.

Objective: To identify the PV issues that most concern to the monitors/project managers in order to find out keys and tools for helping them with the training to investigators and AE management.

Methods: A survey was sent to monitors/project managers of the 29 SCReN research units in order to be aware of their problems regarding PV and to identify the most complicated clinical situations for AE management. We also asked them about the main safety queries and issues observed during AE handling.

Results: A total of 27 surveys were completed representing the 93% of the SCReN research units. The main problem detected at initial visits was the investigator’s lack of time, which makes difficult the correct training in the PV study procedures. The most complicated situations on adverse events reporting were: medication errors, fatal outcomes, scheduled surgeries, endpoints AE or how to manage AE when patients are hospitalized in critical care or present a high morbidity The lack of information on source documents and investigator’s difficulties on filling SAE notification forms are two of the main constraints found by monitors on AEs handling.

Conclusions: Close collaboration between monitors/project managers and PV staff ensures specific training for investigators. In this way, they should be provided with tools that promote their participation in AE management. Applying a risk proportionate approach for safety reporting is essential to facilitate PV tasks ensuring an adequate risk assessment improving patient’s safety.

**CP33 | Role of pharmacological interactions in the myopathy associated with statins**

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Objectives: Simultaneous treatment with statins and other drugs can increase the risk of muscular toxicity. The aim of this study was to analyze the different types of myopathy related to the treatment with statins and the relative role of pharmacological interactions in their development, according to the clinical cases published.

Methods: A search in MEDLINE/PubMed database, from the 01/01/2015 to 31/12/2017 was performed, using the Mesh descriptors: “Hydroxymethylglutaryl-CoA Reductase Inhibitors” and “Muscular Diseases” or “Mitochondrial Myopathies” or “Myositis” and “Case Reports”, and published in English, French or Spanish. Articles with scarce information or without at least one clinical case were excluded. In each case reported we analyzed: (a) type of myopathy, (b) statin (dose) involved, (c) concomitant medication, (d) presence or absence of potential drug-drug interactions and (e) mechanism involved.

Results: 32 clinical cases included in 32 articles were reviewed. Muscular toxicity reported in them was: 15 cases of rhabdomyolysis, 9 of necrotizing autoimmune myopathy, 7 of myositis and 1 case of myalgia. In 11 (34.4%) of the
cases studied, some pharmacological interaction was potentially increasing the muscular toxicity of statins. Of the total of the interactions found, 8 (72.7%) were cases of rhabdomyolysis and 3 (27.3%) myositis. Drugs involved in these interactions with statins were: macrolides [erythromycin (n = 1), clarithromycin (n = 1)], fusidic acid (n = 1), ciprofloxacin (n = 1), fluconazole (n = 1), cyclosporine (n = 1), colchicine (n = 1), ezetimibe (n = 2) and ticagrelor (n = 2). The mechanisms involved in the interactions were mainly pharmacokinetics and information about them was included in the Summary Product Characteristics of the medicines.

Conclusions: Pharmacologic interactions seem to play an important role in the development and severity of muscular toxicity associated with statins. All of the interactions found were well-known and should be remembered during the prescription of statins, in order to prevent new cases of myopathy.

CP34 | SGLT2 inhibitors and bladder cancer: analysis of cases reported in the European pharmacovigilance database (EUDRAVIGILANCE)

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Objectives: The association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and bladder cancer remains uncertain. This study aimed to evaluate the existence of a possible safety signal of bladder cancer associated with SGLT2 inhibitors.

Methods: We searched for all suspected cases of bladder cancer (‘bladder neoplasms malignant’ now being the High Level Term, included in MedDRA, Medical Dictionary for Regulatory Activities, version 21.0) up to 5 June 2018, associated with SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin) in EudraVigilance. To assess the association between bladder cancer cases and each SGLT2 inhibitor we calculated the Reporting Odds Ratios (RORs), a measure of disproportionality similar in concept to the relative risk ratio.

Results: Among 5 653 097 events of all types recorded in EudraVigilance, we found 9711 (0.17%) cases of bladder cancer. 90 of those cases were related to SGLT2 inhibitors. The mean age of patients was 65.7 ± 9.6 years (range 49-85 years; 33, age not specified); 82.2% male (4.4%, sex not specified). 52 cases were identified for dapagliflozin, 24 for canagliflozin and 15 for empagliflozin (a patient took canagliflozin and empagliflozin). The latency period was mentioned only in 30 cases, with a median until bladder cancer appearance of 320 days.

The ROR for pooled SGLT2 inhibitors was 3.65 (95% CI 2.96-4.49). The 3 SGLT2 inhibitors drugs fulfilled the safety signal criteria. The association was strongest with dapagliflozin (ROR 5.84, 95% CI 4.44-7.68) than with the rest of SGLT2 inhibitors: canagliflozin (ROR 2.48, 95% CI 1.66-3.71) and empagliflozin (ROR 2.39, 95% CI 1.44-3.97). Nevertheless, it is important to recall that this disproportionality should only be considered exploratory in the context of signal detection, as it does not allow quantification of the true risk.

Conclusions: Data from EudraVigilance confirm this safety signal. Thus, physicians who prescribe SGLT2 drugs should monitor their patients, and inform about the risk of this serious adverse reaction.

CP35 | Safety of treatment with biologic agents in a general hospital: preliminary data

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Objectives: The aim this study was to detect any unanticipated adverse drug reactions (ADR), especially severe reactions; characterize the frequency and occurrence of ADR in clinical settings; and identify factors that may affect the safety and effectiveness of biologics agents in a tertiary Hospital.

Methods: This was an observational study to assess the safety of therapies with biologic agents used in Alicante General Hospital. Patients who start or change biologic treatment from 01 January-28 February 2017 were included and followed up for 41 week. All treatments were approved by the biologic committee. Investigator completed a case report form for each patient from medical record describing clinical findings observed. ADR defined as all adverse events (AE) for which the causal relationships determined by Naranjo & Karch-Lasagna (KL) score were possible/probable. ADR were described according to system organ classification.

Results: A total of 91 patients were enrolled with a mean age of 46(16.13) range [2-79]; 49% were female and the most frequent diagnoses were Psoriasis (18.6%) and Crohn’s disease (13%). 61% of patients had illness > 5 years, 47% had received prior treatment with biologics drugs and 43% used concomitant drugs. Adalimumab
(21%), secukinumab (11%) and rituximab (10%) were the most frequent biologics agents used. All doses used were according to the label. We detected 145 AE in 60 (66%) patients of whom 20 (30%; 20/60) suffered severe AE. Infection was the most frequent AE 33.8% (49/145), followed by neuro-psychiatric disorders (16.6%; 24/145). There was 1 case of breast carcinoma, 1 case of skin carcinoma, and 1 case of infusion-related reaction. Naranjo score detected 21.4%(31/145) probable ADR, while KL score identified only 6 cases as probable or defined ADR 4%(6/145).

Conclusions: There is high discordance between current causality methods to determinate causality relationships in biologics ADR. We need develop specific algorithms for these drugs.

CP36 | Comparing methods for detection of aDR based on laboratory tests or on clinical documentation review
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Objectives: To compare a method for the detection of ADR based on a complete review of all clinical documentation, including laboratory tests (Method A) against the simulation of other detection method based on the identification of abnormal values of laboratory tests (Method B).

Methods: For the period 2011-2017, all discharge reports, and full clinical records of patients, generated by four clinical departments of the "Complejo Hospitalario Universitario de Canarias", were retrospectively assessed in order to identify possible cases of ADR (Method A). A secondary analysis of the reports was focused on the possibility that laboratory tests could be sufficient to identify the ADR previously found (Method B). The identified ADR were classified according to the MedDRA dictionary (System Organ Class SOC).

Results: Method A allowed the identification of 365 cases (out of 11,283 clinical records reviewed), while with method B only 198 of them would have been identified, missing all cases corresponding to the skin, immune system, cardiac, ear, psychiatric and general disorders SOC terms. For neurological alterations the percentage of cases identified by the method A was 10% but it was only 1% if using exclusively laboratory test (method B). Similarly, vascular disorders fell from 6% to 1%. However, for blood and metabolism disorders a total of 135 cases were identified that represents 37% of all ADR identified by method A but up to 67% of the cases identified using only lab tests.

Conclusions: The use of a method exclusively based on the detection of abnormal laboratory findings leads to an overestimation of some types of ADR and an underestimation of other types of ADR. It’s necessary to search cases through a global assessment of the clinical documentation to perform a more realistic pharmacovigilance program.

CP37 | Severe and moderate hyponatremia in a tertiary care hospital: comparison of incidence and causes
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Objectives: The aim was to evaluate the incidence of severe-hyponatremia (SH, serum-sodium-level<116 mEq/L) and moderate-hyponatremia (MH, serum-sodium-level<122 mEq/L) using data from a Pharmacovigilance Program from Laboratory Signals at hospital (PPLSH) and the different causes, as well as the most frequent drugs in drug-induced hyponatremias (DIH).

Methods: During a ten-year period (July 2007 to June 2017) all admissions from all causes were monitored by PPLSH. Patients who died in the Emergency Department (ED) were also included. Cases with Serum Sodium (SS) <116 mEq/L were detected in the first period (July 2007 to June 2012), cases with SS<122 mEq/L were detected in the last period (July 2012 to June 2017).

The incidence rate of DIH in each group and other aetiologies were calculated (two-sided-Poisson 95% CI) and frequency of drugs according to the Anatomical Therapeutic Chemical (ATC) Classification System were calculated in both groups. Chi-square test were used to compare the frequency of drugs per group.

Results: In the first 5-year period, there were 238 311 hospitalizations, and 505 cases of SH. The SH-incidence was 17.37/10,000 patients (Poisson 95% CI: 10.67-27.22). Drug-induced-SH was the third most frequent cause of SH, incidence of 3.02/10,000 patients (Poisson 95% CI: 1.08-8.77) after of bleeding/CNS masses (3.19x10,000 patients Poisson 95% CI: 1.08-8.77) and neoplasia (3.11x10,000 patients Poisson 95% CI: 1.08-8.77).

- In the last 5-year period, there were 225 862 hospitalizations, and 1021 cases of MH from admitted patients and deaths in the ED. The MH-incidence was 40.11/10,000 patients (Poisson 95% CI: 29.42 to 54.47). Drug-induced-
MH was the most frequent cause of MH, incidence of 14.74/10,000 patients (Poisson 95% CI: 8.40-23.49). There were 151 culprit drugs in the SH-group and 635 in the MH-group. The most frequent therapeutic groups were cardiovascular system (50.33% vs 60.79%, \( P = 0.019 \)) and nervous system (32.45% vs 19.69%, \( P = 0.001 \)). The most frequent drug in both was Hydrochlorothiazide (15.27% vs 18.27%, \( P = 0.379 \)).

**Conclusions:** Due to the incidence of severe and moderate drug-induced hyponatremias and the fact that thiazides and other CS drugs, as well as NS drugs are frequently prescribed, a deprescribing or a careful monitoring must be done in order to prevent hospitalizations.

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**CP38**  |  **Caffeine-halothane contracture test and pharmacogenomics screening for investigation of malignant hyperthermia susceptibility**

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**Objectives:** Malignant Hyperthermia (MH) is a life-threatening pharmacogenetic disease with crises triggered in susceptible individuals (MHS) by exposure to halogenated general anesthetics. The aim was to find in the available literature preemptive methods to avoid this disease, and to elucidate which centers perform those tests.

**Methods:** The Department of Anaesthesiology of our center requested information about a technique called Caffeine-Halothane contracture test (CHCT) and its possible application in our clinical practice. A review about this adverse reaction and tests was made.

**Results:** We found out a European group dedicated to this issue. The European Malignant Hyperthermia Group (EMHG) has accredited laboratories in Germany, Netherlands, Denmark, Sweden, UK, Israel, Australia, New Zealand, South Africa and Brazil. In 2015 new guidelines for investigation of MHS using the CHCT and DNA-based screening were published. RYR1 was found to be the major locus implicated in MH, being CACNA1S the second locus. The CHCT is not a screening test and is poorly predictive of MHS when applied to the general population because of the low prevalence of the disorder, but it has excellent predictive value when used in patients with: familiar history of MH, adverse reaction to general anaesthesia, recurrent rhabdomyolysis or myopathy and idiopathic hyperCKaemia. New EMHG testing guidelines consider DNA-screening as primary diagnostic approach to the CHCT. When DNA-screening does not prove susceptibility, then CHCT is performed, with a specificity of 94% and sensibility 99%, classifying patients based on MHS by measuring the contracture intensity of fresh muscle biopsy in response to these drugs. Although the mortality has decreased since the use of dantrolene (from 75% to 5%), it is still a potentially evitable cause of death.

**Conclusions:** Taking all this into account, and being no centers in Spain performing these techniques, it would be interesting to create a reference center in our country to avoid this life-threatening disease in susceptible patients.

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**CP39**  |  **Anticonvulsant hypersensitivity syndrome (AHS), report of a case**

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**Objectives:** To do a review of the AHS, its frequency, and the importance of knowing it to make a fine and fast differential diagnosis in patients who present it to avoid fatal outcomes.

**Methods:** AHS is a rare (incidence: 1/10,000 to 1/10,000) and severe syndrome (mortality rate: 10%) that occurs within 3 months after the beginning of antiepileptic treatments, especially with aromatics: phenytoin, phenobarbital or carbamazepine.

The characteristics of this syndrome include: fever, severe skin involvement, lymphadenopathies, internal organs involvement (as liver) and eosinophilia.

We report a representative case of AHS during treatment with different antiepileptics.

**Results:** A 59-year-old male patient diagnosed with primary cerebral non-Hodgkin's lymphoma in 2006 undergoing holocranial chemotherapy and radiotherapy, developed a post-radiotherapy leukoencephalopathy. In February 2017, he's diagnosed of left fronto-temporal symptomatic focal epilepsy, and Levetiracetam is started: developing, after two loading-doses of 1 g, a facio-thoraco-abdominal exanthema; corticoid and anti-histamine oral treatment is established. Levetiracetam is replaced by Lacosamide 100 mg/12 h v.o.

In January 2018, he attends the A&E due to new crisis; Lacosamide is removed and Valproate is initiated (1500 mg/day). After 24 h, he has a generalized-rash. Valproate is suspended and Lacosamide is reintroduced. In March 2018, he presents a new crisis. Lacosamide is suspended and Phenytoin is started (loading dose: 1 g, afterwards: 250 mg/day orally). After 4-day treatment, he
presents a generalized rash and leukopenia/eosinophilia, without impaired liver function, and he receives Dexchlorpheniramine and Methylprednisolone. Phenytoin is suspended, replacing it by Clobazam (10 mg/12 hours). The Allergy Service diagnoses him from DRESS Syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) and recommends putting off the introduction of a new antiepileptic until rash and eosinophilia resolution. The high rate of cross-reactivity between antiseizures (>75%) suggests relationship between previous episodes.

**Conclusions:** Signs of alarm in patients on treatment with antiepileptics that may suggest an AHS are: rash, fever, lymphadenopathies, increased transaminases. In this situation, the drug should be suspended. The knowledge of this entity can avoid fatal outcomes.

**CP40 | Systematic review of pharmacovigilance studies in pediatric oncohematology**

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**Objectives:** 2-5% of hospital admissions in children are related to an adverse drug reaction (ADR). Incidence in hospitalized children can range from 0.6% to 17.7%. Although drugs used in oncology are defined as a risk factor for ADRs, and ADRs are frequent in oncological inpatients, there are few studies focusing on this specific population. Our aim is to summarize the studies available, describing the methodology used and the results.

**Methods:** A systematic search was performed on PubMed using both free terms and combinations of MeSH terms. Studies describing ADRs in oncohematological pediatric patients were included. Studies limited to a specific drug or descriptions of infectious outbreaks were excluded. Bibliography used in the selected articles was also reviewed and included if it met the inclusion criteria.

**Results:** 12 articles were included. 5 articles were retrospective cohort studies and 7 were prospective. Different methodologies were used to identify ADRs: strict monitoring of patients and review of clinical courses, investigation of the use of antidotes that could indicate the presence of a side effect, analysis of prescription and/or patients’ registers, or other methodologies. Prospective studies in hospitalized oncohematological patients have shown an ADR incidence between 56% and 65%, and hospitalization was due to an ADR in 22% to 68% of patients. Despite of methodological differences, 4 studies assessed preventability of the ADR, ranging from 20.7% to 64%.

**Conclusions:** There are few studies describing side effects in this population of children, even though oncohematological pediatric patients are at high risk of side effects because of the high number of drugs used and their toxicity. The methodology used and the results obtained are very heterogeneous.

**CP41 | Sudden cardiac death and drug in epidemiological studies: a systematic review**

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**Objectives:** Drugs have been frequently associated with sudden cardiac death, and this association has led to the withdrawal or the restriction of use of several medicines. The autopsy is a definitive tool to establish the etiological diagnosis of sudden cardiac death. Several epidemiological studies have been published to assess the risk of sudden cardiac death associated to the use of different drugs. Our aim is to describe the main methodological characteristics used in these studies mainly focusing on the study design and the source of information regarding exposure and outcome. Moreover, the drugs and the risks described in the bibliography will be summarized.

**Methods:** A systematic search was performed on PubMed with a defined search strategy. Epidemiological studies evaluating sudden cardiac death associated to the use of drugs were included; description of cases or series of cases were excluded. No other filters or limitations were applied. Bibliography used in the selected articles was also reviewed and included if it met the inclusion criteria, in order to assess the more studies as possible.

**Results:** 52 articles were included. 19 (36.5%) of them were case-control studies and 18 (34.6%) were cohort studies. 32 studies used databases (Medicaid, CPRD, GPRD, IPCI); only 8 studies included autopsy results. Drugs that showed a high risk of sudden death were antidepressants, antipsychotics, antibiotics, stimulants, domperidone and others (flecainide, spironolactone + cotrimoxazole, terfenadine + ketoconazole, etc); 8 studies did not show a significant increased risk (astemizole, cisapride, fluoxetine, ziprasidone, propoxifen).

**Conclusions:** Most studies performed with databases are observational, and its important limitation is the lack of the autopsy confirmation. Drugs described are known to prolong QTc interval as described previously.
Multidisciplinary interoperability in the development of a hospital-based pharmacovigilance unit

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Objectives: To describe the impact of a multidisciplinary approach in the development of a Pharmacovigilance programme at Hospital Clínic de Barcelona.

Methods: The Pharmacovigilance programme was developed in a step-wise fashion, based on:
- The creation of a multidisciplinary team (evaluation team: Clinical Pharmacology, Clinical Pharmacy, Allergology, Dermatology, Preventive Medicine; medical informatics and information systems (MIIS); administrative support (AS))
- The establishment of objectives
- The measurement of key performance indicators (KPIs).

Conclusions: The described multidisciplinary interaction has been key to develop the pharmacovigilance program. The low number of reported ADRs (n = 22) shows that a “notification culture” of spontaneous voluntary reporting still has to be further promoted. Complementary methods of capturing ADRs will be considered for subsequent phases of the program.

Results:

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CP43 | Adverse drug reactions detected using global trigger tool in patients undergoing surgery
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Objectives: To determine the prevalence of adverse drug reactions (ADR) in patients undergoing surgery requiring hospitalization using a modified Global Trigger Tool (GTT).

Methods: A retrospective study was conducted in a tertiary care hospital with a random sampling of 120 patients undergoing surgery between January and June 2017. Excluded patients were younger than 18 years old, hospitalized for less than 24 hours and undergoing organ transplantation as well as obstetric, dermatological or ophthalmological surgeries. Medical records were screened by trained nurses and quality medical specialists. Care, Surgical and Medication modules of the GTT were used to identify harms. However, triggers referring antiemetic agents (M10) or hypotension (M11) were not assessed because both are frequent in operated patients due to the anaesthetic and opioids used. All drug-related triggers (M triggers and those suggesting an ADR) were assessed by a clinical pharmacologist and agreed by surgeons.

Results: Of 120 reviewed surgical processes, 18 triggers were detected suggesting a potential ADR (11, 61% were M triggers). Nine ADR were identified in eight patients (5 ADR from a drug-related trigger, 56%). The prevalence of ADR was 6.7% (8/120). The median age of patients was 69.5 years (ranging from 46 to 83) and 62.5% were women (5). The most frequent ADR were haemorrhages (56%, 5/9) and liver injury (22%, 2/9). None ADR was life-threatening or fatal, and mostly were severe or moderate (44% each, 4/9). The most frequently involved drugs were enoxaparin (in 5 patients) and beta-lactam drugs (in 3).

Conclusions: Half of the detected patients with a drug-related trigger presented an ADR. The positive predictive value of Medication triggers was 45% and its sensitivity was 56%. Therefore, the use of a modified GTT to identify ADR in surgery departments was useful and can provide information about ADR in this patient population.

CP44 | Nervous system disorders associated to tocilizumab: a case report of reversible cerebral vasoconstriction syndrome (RCVS)
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Objectives: Establishing the causality relationship between RCVS and the use of tocilizumab through a case report study.

Methods: We describe a 53-year-old woman with previous history of rheumatoid arthritis, treated with a weekly dose of 162 mg of tocilizumab, an inhibitor of IL-6 receptor used in inflammatory diseases, who presented a reversible vasoconstriction syndrome. The patient therefore developed a cerebellar stroke as the major complication of the vasoconstriction syndrome.

Results: CT scan and MRI showed bilateral cerebellar lesions. Cerebral arteriography showed stenosis and morphology irregularities in both middle cerebral arteries’ distal parietooccipital branches. No infection signs were found spinal fluid. Applying the Spanish Pharmacovigilance System algorithm the case is considered as probable. Following the suspicion of an Adverse Drug Reaction (ADR), the treatment was suspended; the patient was treated with double anti-aggregation therapy and the symptoms gradually disappeared. The ADR was notified to (ID# ES-AGEMED-911661344). A later cerebral arteriography showed total recovery from previously viewed vascular abnormalities. A control MRI showed a chronically established ischemic lesion in both cerebellar hemispheres.

Conclusions: Tocilizumab could be a trigger of cerebral vasoconstriction syndrome. It is important to bear in mind the role of tocilizumab as a possible precipitating factor in order to remove it prematurely and reduce complications such as strokes. It is to our knowledge the first reversible vasoconstriction syndrome possibly precipitated by tocilizumab published to date.
CP45 | Pharmacovigilance applied to autistic spectrum disorder (ASD) with intellectual disability associated

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Objectives: To analyze the clinical improvement after initiating a pharmacovigilance program in the population with Autism Spectrum Disorder (ASD) and intellectual disability.

Methods: An ambispective study was carried out, in 83 patients, from four centers of special education in Alicante. We analyzed demographic and clinical data (comorbidities, personal history), along with the record of suspected adverse drug reactions (ADR) and drugs potentially associated with the ADR found (antipsychotics, anticonvulsants, antidepressants and anxiolytics).

Results: In the ASD subjects (30 ± 10 years of age, 86% men), the median number of medications was 4 (IQR: 3-5) being 48% antipsychotics, 22% anticonvulsants, 16% anxiolytics and 12% antidepressants. In addition, comorbidities 3 (IQR: 2-4), the most frequent being insomnia, epilepsy and psychotic agitation. A total of 64 suspicions of ADR were reported mainly from the nervous system (25%), metabolic diseases (25%) hypercholesterolemia (17%), extrapyramidal (12%) and constipation (11%). The pharmacological group most associated with a higher causality were antipsychotics (52%). Most were mild and resolved with the withdrawal of the medication.

Conclusions: The pharmacovigilance program developed in the ASD and intellectual disability population facilitated the recording of suspicion of ADR together with its pharmacological approach and resolution. The next step will be to assess the prevention of them, along with the analysis of potential interactions and the introduction of genetic markers, to favor a more personalized medicine in this vulnerable population.

CP46 | Endocrine disorders in children and adolescents treated with antipsychotics. Sentia pharmacovigilance Spanish Registry

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Objectives: Second generation of antipsychotics are associated with endocrine side-effects. There is concern about the occurrence in children and adolescents of endocrine adverse events such as hyperprolactinemia. Hyperprolactinemia could produce suppression of gonadotropin releasing hormone secretion and hypogonadism. The aim is to analyze analytical endocrine parameters such as thyroid hormones (TSH, T3, and T4), prolactin and sexual hormones (FSH, LH, 17 OH Beta, estradiol, 17 OH Progesterone and Testosterone) in children and adolescents treated with antipsychotics and followed through the SENTIA Registry.

Methods: SENTIA is an online registry (https://sentia.es) for long-term pharmacovigilance of antipsychotics in children and adolescents. Children and adolescents antipsychotic-naive are monitored before treatment and at 1, 3 or 6 months after starting treatment. Patients who enter into the registry already being treated for more than one month are monitored on a 6-monthly basis. Monitoring at 1, 3 and 6 months is also carried out when there is a change in antipsychotic treatment. Endocrine parameter abnormality is defined as any value out of local reference range at any single visit.

Results: 128 patients were included in this study, 75% male, average age 11.9 ± 3.04 years, 48% under 12 years. Median time of follow-up was 16.3 ± 15.7 months, with a median of 11.1 months (1-67 months).

Abnormal endocrine parameters during AP treatment were found in 92.2% patients, mainly hyperprolactinemia (45.3%), high T3 (43%), and low testosterone (30.5%). In 74 (62.7%) patients, abnormal endocrine parameters were accompanied by clinical metabolic or endocrine manifestations. 9.3% of the patients were referred to the pediatric endocrinologist. There were no treatment discontinuations due to endocrine abnormalities.

Conclusions: Alterations in analytic endocrine parameters are very frequent in children receiving antipsychotics. The results showed that in the short term; the endocrine
alterations did not have clinical relevance. The consequences in the long term remains unknown. Therefore, the follow-up of this population to monitor possible clinical consequences of these alterations in the long term is necessary.

**CP47**  | Association between potentially inappropriate prescriptions according start-stopp criteria and clinical significant outcomes in elderly inpatients

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**Objectives:** Elderly people suffer physiological changes that generate pharmacokinetic and pharmacodynamic alterations, also have multiple co-morbidities and subsequent polypharmacy, which place them at higher risk of inappropriate prescribing (PPI), with increased risk of adverse drug reactions and consequently higher rates of morbimortality. As a result, screening tools have been developed to prevent this inappropriate prescribing and help clinicians improve their prescribing. One of them is STOPP/START criteria. Their use has allowed the reduction of adverse drug reactions in ambulatory units, but there are few studies that have evaluated their clinical impact in inpatients, who are more vulnerable.

To determine the association between the potentially inappropriate prescriptions (PPI), according to the STOPP/START 2015 criteria, with clinical outcomes in hospital patients (death, falls or transfer to greater complexity) and within 30 days after discharge (death, falls, emergency visit or hospital readmission) in elderly inpatients with a acute medical disease.

**Methods:** A cross-sectional study was carried out, including inpatients older than 64 years. We excluded patients with surgical disease and life expectancy <30 days. We applied STOPP-START criteria during hospital stay and discharge data.

**Results:** 230 inpatients were included. The total of medicines prescribed was 3096. 72.6% of patients showed at least one PPI during hospital stay or at discharge. Median number of PPI per patient was 1.78. The presence of PPI during hospital stay and after discharge was not associated with clinical outcomes.

**Conclusions:** STOPP-STAR criteria allow the identification of a high number of PPIs in inpatients. Despite the possibility of serious drug induced injury and associated risks, there was no evidence to endorse the use of this tool to prevent significant clinical consequences. Future studies are necessary to evaluate the clinical impact of PPI in hospitalized patients and to define the best tools for this purpose.

**CP48**  | Lactic acidosis induced by linezolid in renal impartment

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**Objectives:** Lactic acidosis is a relatively rare but life-threatening adverse drug reaction (ADR) of various medication classes. If there is no apparent medical cause for hyperlactatemia (sepsis, hypotension, hypoxia), clinicians should consider a medication etiology.

**Methods:** A 76-year-old male with hypertension, dyslipidemia, diabetic and allergic to beta-lactamics, carrier of right knee prosthesis since 14/11/2017, on 09/04/2018 he begins with pain, flushing and functional impotence at that level. On 12/04/2018, prosthesis was removed, a spacer was placed and daptomycin was started against infection sensitive S. epidermidis. On 17/4/2018, treatment with oral rifampin was started. On 07/05/2018, a change from daptomycin to oral linezolid was made due to poor evolution (renal failure, possible nosocomial pneumonia). On 12/05/2018 he presented worsening of his situation with low level of consciousness and respiratory difficulty, acidosis, hyperlactatemia and hyperkalemia. In the following days, despite the adjustment of serum and bicarbonate, clinical and analytical worsening continues. On 15/05/2018, he died in the context renal failure, lactic acidosis and hyperkalemia. Clinical pharmacology department was interconsulted for a suspicion of an ADR to assess the possible causality of medication. The algorithm of causality of the Spanish pharmacovigilance system was applied, we made a review of the Summary of Product Characteristics and of the scientific literature of the drugs involved.

**Results:** There is a probable causality to linezolid, being negative for the other drugs. The lactic acidosis is found in the SPC of linezolid, as well as case reports, although longer treatments are usually detailed.

**Conclusions:** Linezolid is a useful option in the patients who, due to allergic reactions, intolerance or bacterial resistance, cannot be treated with vancomycin or other antibiotics, without contraindication to its use in renal impairmt. However, linezolid-induced lactic acidosis is associated with renal insufficiency. Therefore, close monitoring of kidney function and serum lactate is recommended from the beginning of linezolid therapy.
**CP49 | Kounis syndrome in a newborn**

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**Objectives:** The Kounis syndrome is defined by symptoms and cardiac signs caused by inflammatory mediators, grouped in vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis, but the pathogenic mechanism is unclear: mast cell mediators in the pathogenesis of coronary spasm or a hemodynamic stress of the acute reaction has long been hypothesized.

**Methods:** Neonate with hypoplastic left ventricle requiring 2 stent (one in the ductus made of Ni-Ti, another in the isthmus made of stainless steel), with multiple complications including thrombosis of the right carotid, requiring anticoagulation with heparin. Subsequently, he periodically develops episodes of ischemia with low expenditure (secondary ischemic hepatitis, bradycardia, poor perfusion, desaturation, elevation of troponin and NT-proBNP). Coronary alterations and rapid worsening of heart disease are ruled out. Clinical pharmacology department is interconsulted for suspected anaphylactoid drug process, for which we apply the algorithm causality of the Spanish pharmacovigilance system.

**Results:** We found possible causality (time line and biological plausibility) for stents, heparin, esmolol, vancomycin and cefotaxime, so its suspension was recommended. No new events appear (another antibiotic therapy was used, heparin was replaced by fondaparinux). Skin test was performed on nickel and titanium being negatives. Basophil activation (BAT) and lymphocyte transformation (LTT) tests were performed for the suspected drugs, being BAT was not titrable and LTT was positive for heparin. A new dose of heparin was readministered by an error, after that a new ischemic episode was developed (positive rechallenge), with which the causality of the algorithm would rise to definite.

**Conclusions:** To our knowledge it is the first case described of Kounis angina in a newborn. The Kounis syndrome is a diagnostic challenge even more if it occurs in a critical ill neonate. In its diagnosis, the clinic, the causality algorithms and in vitro tests to evaluate the culprit drug and different mechanisms of the reaction should be considered.

**CP50 | Serious adverse events in healthy volunteers identified during clinical trials**

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**Objectives:** To describe the main characteristics of serious adverse events (SAEs) in healthy volunteers, performed in Centre d’Investigació de Medicaments (CIM) from January 2007 to December 2017.

**Methods:** AEs (according to the European Union’s criteria) in healthy young volunteers identified in the CIM were studied. The variables evaluated were age and sex of the volunteers, the reported adverse event (AE), their seriousness and outcome and the suspected drugs.

**Results:** In this period, 82 clinical trials were performed (bioequivalence 59%; safety and tolerability 27%; pharmacodynamics 7%; pharmacokinetics 5%) and were identified 1624 AEs in 799 volunteers (52% female vs 48% male). Six of them (0.37%) were serious and described in this study; the most common group of age was young (median age of 27); 83% were female. The 6 SAEs reported were neuromuscular (66%), renal and urinary (17%) and immune system disorders (17%). Only 2 were related to study drugs (phosphodiesterase PDE10 inhibitors and thiazidic diuretic). The outcome for all SAEs was a full recovery without sequelae.

**Conclusions:** Eighty two clinical trials were performed in 11 years in CIM Sant Pau and only 6 SAEs were reported. Two were suspected to be related to the study drug.

**CP51 | Usefulness of case reports for categorization of drug hepatotoxicity potential**

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**Objectives:** A recent publication categorizes hepatotoxicity potentials of drugs listed in the LiverTox© website into 5 categories based on number of published case reports (Björnsson & Hoofnagle, 2016). We aimed to test the accuracy of this categorization by applying it to cases in the Spanish DILI Registry.
Methods: We applied the 5 categories (A: $\geq$50 reports; B: 12-49; C: 4-11; D: 1-3; E: none) to 187 causative drugs from 829 cases in the Spanish DILI Registry. We also collected information about drugs causing DILI and acute liver failure (ALF) from Spanish, SLATIN, DILIN and Iceland registries and other ALF DILI cohorts (Suzuki et al 2010, Reuben et al 2014, Devarbhavi et al 2017, Russo et al 2004). Results: Thirty-six drugs (19%) in the Spanish registry were classified as category A, 42 (22%) as B, 39 (21%) as C, 17 (9.1%) as D and 14 (7.5%) as E. Thirty-nine (21%) drugs (e.g. chloromiazole) were unclassified. Outcome data were compared between A/B and C/D groups (high vs low hepatotoxicity potential). Cases caused by C/D drugs, presented higher severity with more ALF cases than A/B drug cases (7% vs 3%, $P = 0.02$). Orlistat (C) and sibutramine (D) were associated with ALF in the Spanish registry. Drugs that have been withdrawn from the market or with hepatotoxicity safety warnings (e.g. nefazodone and donepezil) were found in category C. In contrast, amoxicillin-clavulanate (A) with the highest number of cases in the database were associated with very few ALF cases. Some drugs in category A (e.g. thioguanine) and B (e.g. heparin) were not present in any published DILI cohorts.

Conclusions: Classification of hepatotoxicity potential based on case report numbers can be misleading and inaccurate regarding DILI risk. A categorization should combine comprehensive information on liver safety regulatory measures, frequencies and drug-induced ALF cases. Funding: AEMPS, FEDER (PI15-01440), CIBERehd-ISCI3.

CP52 | Hypersensitivity and desensitization to monoclonal antibodies

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Objectives: To describe the cases of two patients that exhibited hypersensitivity reactions to monoclonal antibodies (alemtuzumab and vedolizumab, respectively) and underwent desensitization.

Methods: Patient 1 was a 41 year-old man diagnosed with T-cell prolymphocytic leukaemia and he was prescribed alemtuzumab. During alemtuzumab infusion number 18, the patient showed cutaneous eruption with a miliary pattern, despite premedication with corticosteroids and antihistamines. The eruption returned with successive alemtuzumab infusions (infusions 19, 20 and 21), remained present for longer and was more severe with each infusion. Patient 2 was a 38 year-old woman diagnosed with ulcerative colitis, refractory to infliximab and intolerant to azathioprine and sulfasalazine that was receiving treatment with intravenous vedolizumab. Cycles 1 and 2 were well tolerated, but in cycles 3, 4 and 6 she experienced hypotension and dyspnea, in spite of premedication with dexamethasone and metoclopamide. During cycle 6, she also showed facial angioedema, systemic urticarial reaction and oropharyngeal pruritus treated with methylprednisolone and ebastine.

Both cases were notified to the Andalusian Pharmacovigilance Centre.

Results: The patient 1 was referred to the Allergy Unit as it was necessary to maintain alemtuzumab treatment and he underwent alemtuzumab desensitization according to a 12-step protocol. A total dose of 29.09 mg was administered intravenously during a period of 3 h and 47 min at increasing doses, rhythm and volumes. Since vedolizumab was the only therapeutic alternative, patient 2 was planned to undergo vedolizumab desensitization according to one 8-step protocol. Desensitization protocol was performed with a total duration of 4 hours and 35 minutes and a total dose of 293 745 mg. Alemtuzumab and vedolizumab desensitization protocols were safe and well tolerated.

Conclusions: The occurrence of allergic reactions involves the withdrawal of treatment. Desensitization to biological drugs may resolve a therapeutic problem when no other alternatives can be used. Informed consent and a close monitoring are mandatory.

CP53 | Outcomes of pregnancies exposed to methotrexate

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Objectives: Methotrexate (MTX) is a known teratogenic drug in humans, but there is still controversy about the waiting period between the end of MTX’s treatment and pregnancy initiation, also depending on MTX dose. The aim of this study was to evaluate the outcomes of pregnancies exposed to MTX.
Methods: A retrospective observational study of consultations received at the Teratogen Information Centre (TIS) of the Vall d’Hebron University Hospital (VHUH) between January 1, 2005 and December 31, 2016 about pregnancies exposed to MTX, was carried out. Inclusion criteria were consultations about MTX exposure of the woman or of the man, anytime between 1 year before conception and the birth.

Results: Twenty-eight consultations were included. Among the 23 pregnancies with exposed women, the MTX was indicated for treatment of diseases (18 cases; median dose = 20 mg/week) or to induce abortion in ectopic pregnancies (EP) (5; median dose = 84 mg/week). Among the 18 cases the results were 10 elective terminations, 1 spontaneous abortion and 7 live-born children with no malformations. Among the 5 cases of EP the results were 2 spontaneous abortions, 1 elective termination, 1 dead fetus and 1 live-born child with no malformations. In 5 pregnancies with exposed men, MTX was indicated for treatment of diseases (median dose = 20 mg/week) and the known results were 2 induced abortions by fetal abnormality and 2 live-born children with no malformations.

Conclusions: Our findings show a high percentage of live-born children with no malformations in the group of women exposed to relatively low doses of MTX (≤ 20 mg/week). These results could help to provide further evidence that exposition of MTX at relatively low doses during the periconceptional period could be safe in non-planned pregnancies exposed to MTX.

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Objectives: To assess the prevalence, associated factors, adverse drug reactions (ADRs) and the drugs involved related to emergency room (ER) visits and hospital admission.

Methods: Observational and retrospective study of intensive ADRs monitoring patients admitted in ER in a third-level hospital over a two months period in 2017. The primary endpoint was the ADR-related ER visit. A descriptive analysis of age, gender, comorbidities, number of drugs, suspected drugs and the reactions in ADR-related ER visit was performed.

Results: Overall, 352 out of 15 722 ER visits were due to ADRs (prevalence: 2.24% [95% CI 2.20-2.48%]). Mean age (standard deviation [SD]) of patients was 74.7 (15.6) years and 151 (55.3%) were men.

The comorbidities more frequent were: hypertension, diabetes mellitus and atrial fibrillation, and 51.2% of patients had a Charlson Comorbidity index ≥ 3. The mean number of drugs (SD) was 8 (3.7). Most patients (81.8%) were exposed to polypharmacy, and a drug-drug interaction was suspected in 48.3% of cases. Among the patients with documented suspected ADRs, 31.8% were hospitalized. The mean length of stay admissions (SD) was 9.0 (8.2). ADRs-related costs were € 1871.6/ADR.

With regard to severity 68.1% were severe, with a fatal outcome in five patients. The ADRs were mainly type A reactions (94.9%). Gastrointestinal disorders represented the most common ADRs. The drugs most frequently associated with ADRs were antithrombotics, psychoanaleptics and psycholeptics. The most frequent drug-reaction associations were hyposphagma and gastrointestinal bleeding caused by vitamin K antagonists, and hypoglycaemia induced by insulin.

Conclusions: ADRs are a relevant cause of ER visits, and often lead to hospital admission. They are dose-related and predictable in more than 90% of cases. Most cases involve elderly patients with pluripathology and polymedicated, and result from well-known reactions of a few commonly used drugs. ADRs were associated with high costs.

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CP55 | Could a real world data study be conducted with electronic health records from different institutions in our country? The reality of a multicentre case control study

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Objectives: To analyse the feasibility of conducting pharmacoepidemiologic (PE) projects in research units (UICECs) of the Spanish Clinical Research Network (SCReN).

Methods: Step-1 (2014): Survey to assess pharmacoepidemiology (PhV) training and the existence of PhV programmes and useful information systems for research in the UICECs. Step-2 (2015): Survey to assess whether the hospitals had computerised medical records with exportable data on patients’ treatments, diagnosis and laboratory parameters.

Results: Overall, 352 out of 15 722 ER visits were due to ADRs (prevalence: 2.24% [95% CI 2.20-2.48%]). Mean age (standard deviation [SD]) of patients was 74.7 (15.6) years and 151 (55.3%) were men.

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Conclusions: ADRs are a relevant cause of ER visits, and often lead to hospital admission. They are dose-related and predictable in more than 90% of cases. Most cases involve elderly patients with pluripathology and polymedicated, and result from well-known reactions of a few commonly used drugs. ADRs were associated with high costs.
CP56 | Risk of stroke in patients using antiepileptics. A case control study with real world data

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Objectives: To estimate the risk of ischemic stroke in patients with exposure to antiepileptic drugs.

Methods: Population-based, case-control study. Cases were patients with a first stroke episode registered at hospital discharge identified from the Information System for Research in Primary Care (SIDIAP) database from 2009-2015 in Catalonia. Controls were matched 1:10 by sex, age and health area. Information on drug exposure was obtained from invoicing of the pharmacies to Catalan Health Service (CatSalut). Patients with previous history of stroke and age < 18 years were excluded. Multivariate conditional logistic regression models were fitted to estimate adjusted odds ratios of stroke.

Results: A total of 12 616 cases of ischemic stroke were identified and matched with 125 264 controls. Cases showed a higher proportion of cardiovascular comorbidities and co-medications. The mean age was 72.6 (IQR 65-82) years and more cases were classified as high cardiovascular risk patients (n = 2511, 19.9%) than controls (n = 12 467, 10.0%). Mortality within the following year after the index date was higher for cases (n = 2633, 20.9%) than for controls (n = 8168, 6.5%).

The exposure to antiepileptic drugs was associated to ischemic stroke [ORadj 1.4 (95% CI: 1.3-1.5)]. When analyzing by active substance clonazepam and pregabalin did not show a risk for stroke. The highest risk was for levetiracetam [ORadj 7.5 (95% CI: 6.6-8.4)] and the lowest for gabapentin [ORadj 1.2 (1.1-1.3)]. For current users of levetiracetam the risk was ORadj 5.3 (95% CI: 4.2-6.6) and for past users the risk was ORadj 11.2 (95% CI: 9.3-13.5). Monotherapy with levetiracetam was also associated with an increased risk for ischemic stroke [ORadj 2.2 (95% CI: 1.5-3.3)].

Conclusions: The exposure to antiepileptic drugs is significantly associated to an increased risk of ischemic stroke. The highest risk was found for levetiracetam which showed a high risk even when considered as monotherapy and adjusting for all other variables.

CP57 | Hospitalizations for infections in patients treated with biological drugs: a retrospective cohort study

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Objectives: To estimate the annual incidence rate of hospitalizations for infections in patients treated with biological drugs in a university hospital, and to describe the characteristics of these infections and the most commonly involved drugs.

Methods: A retrospective cohort study was conducted. Patients were identified through the admission diagnosis list and linked to biological drugs for autoimmune diseases. They were included if they were admitted to the hospital in 2017 due to an infection and have been treated with biological drugs at least during the previous 3 months. Onco-logic patients treated with biological targeted drugs were excluded.
Results: The incidence of hospitalizations in patients treated with biological drugs was 0.7% (160/23,429), and the incidence of hospitalizations for infections in patients treated with biological drugs was 0.15% (36/23,429). A total of 27 patients treated with biological drugs were hospitalized due to an infectious disease (6 patients were readmitted). Most patients had rheumatologic (69%) or digestive (19%) diseases. The median age of patients was 64.5 years (range 4-81) and 67% were women. The most frequent infections were respiratory (39%), digestive (17%), and urinary (17%) systems. In 44% the implicated micro-organism was not determined and in 39% a gram negative bacteria was isolated. Viruses caused 17% of the infections. The most frequently involved drugs were certolizumab (25%) and infliximab (19%). Concomitant immunosuppressive drugs were present in 75% of infections (glucocorticosteroids in 50%). All but two patients recovered, one patient presented neurological sequelae due to meningoencephalitis and another died due to abdominal sepsis.

Conclusions: Almost one out four hospitalizations of patients treated with biological therapy was due to an infectious disease. Incidences rates were underestimated since oncoligic patients were not included in this study. Studies with larger number of patients are necessary to define the size of the problem and to develop preventive strategies.

Results: A total of 27,860 out of 156,547 (17.8%) unique ADRs reports included at least one biological as suspected drug. Batch numbers were not available for 65.6% of ADRs reports with a suspected biological. Consumers were most likely to report batch numbers for suspected biologicals (46.9% ADRs reports). Marketing authorisation holders were less likely to report batch numbers (14.1% ADRs reports). Regarding biologicals with biosimilars already on the market, mean availability of batch number was 16.14% (range 1.27%-27.34%). For infliximab, batch number was only available in 4.23% and 5.89% ADRs reports for opportunistic infections and tuberculosis, respectively, after the marketing of biosimilars.

Conclusions: This study underlines the need for improving traceability of biological medicinal products. Results are consistent with previous publications in the field and raise doubts on the usefulness of routine pharmacovigilance as a valid tool to monitor and identify particular safety issues related to a given biological medicine.

**CP58 Traceability and usefulness of the spontaneous reporting system in the surveillance of biological medicines**

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Objectives: Background Some adverse drug reactions (ADR) to biological treatments could be product or batch related, due to small differences or changes in the manufacturing process. Adequate batch number or tradename identification in ADR reporting should be readily available in systems for postmarketing safety surveillance of biologicals.

Objectives The main aim of this study was to evaluate the traceability of biologicals in Spain via the spontaneous reporting system (SRS). The usefulness of routine pharmacovigilance on the follow up of events of special interest of biologicals was a secondary objective.

Methods: A cross-sectional study was conducted over the period 1/01/2006-31/12/2017, including ADRs spontaneous reports from the Spanish national adverse reactions database (FEDRA). Traceability of biologicals, including by type of reporter, was evaluated. For biologicals with biosimilars on the market, the identifiability of the product (i.e. the possibility of distinguishing the actual biological medicinal product involved) was determined.

**CP59 Relationship of acute kidney disease and metformin induced acidosis**

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Objectives: The experience of the Pharmacovigilance Center of Canary Islands supports the idea that in almost every case of acidosis with lactacidemia attributable to metformin exists an acute deterioration of the renal function. We aimed to check out if that statement corresponds with what was really happening.

Methods: In a retrospective descriptive analysis cases of acidosis in patients from the “Complejo Hospitalario Universitario de Canarias” between the years 2013 and 2014 were identified through the analysis of the MBDS (Minimal Basic Data Set) and the requests to the central laboratory. Lactacidemia (venous lactate level> 2.7 mmol/ L) at admission and ambulatory use of metformin were checked in each case and if both items were present the causal relationship between metformin and acidosis was independently assessed by five investigators.
Results: A total of 467 cases of acidosis were identified. Metformin was suspected of causing acidosis with lactacidemia in 20 of these (Lactate from 3.6 to 18.3 mmol/L, mean 7.95 mmol/L).

In 85% of the cases (17 out of 20) the patients had creatinine plasmatic levels suggesting a renal failure (from 1.8 to 17.9 mg/d/L).

Conclusions: The development of acidosis with lactacidemia by metformin seems to be related to an acute deterioration of the renal function so the use of metformin should be cautious or even disappointed in patients who can easily develop an acute renal failure.

SECTION: D. DRUGS UTILIZATION STUDIES, PHARMACOECONOMICS

CP60 | Use of oncologic and oncohematologic drugs in a tertiary hospital in 2017

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Objectives: To describe drug requests in special situations (DRSS) for oncologic and oncohematologic drugs in a tertiary hospital in 2017, classifying them into categories according to the state of authorization, commercialization, approved indications, and financing.

Methods: All DRSSs reaching the Clinical Pharmacology Service were included. The categories defined were: MAF-HC (high-cost medicine authorized in Spain and financed), OLU (off-label use), MA-PPF (medicine authorized in Spain-pending price and financing), FM-ANC (foreign medicine—authorized in Spain but not commercialized), FM-NA (foreign medicine—not authorized in Spain) and MNA-Inv (medicine not authorized in any country, and which is under investigation). The association between the variables diagnosis by system and category of drug was studied by Fisher's test and association plots.

Results: A total of 92 medicines were evaluated. The most common therapeutic subgroups were antineoplastic agents (L01) in 33 reports (36%), followed by drugs used in diabetes (A10) in 10 (11%) and immunosuppressants (L04) in 9 (10%). New approved medicines were considered added value in 32 (35%) cases, nine of which were the first approved drug for the condition. In a bivariant analysis, factors related to relevant added value medicines in comparison with those without were: being the first approved drug for the condition (81.8% vs. 27.2%; P < 0.001), having either a higher efficacy than control groups in clinical trials (100% vs. 0%; P < 0.0001) or a benefit in subgroups of patients (62.5% vs 37.5%; P = 0.001) and having a higher benefit compared to the available alternatives for the condition (96% vs. 4%; P < 0.0001). On the contrary,

CP61 | Assessing the added value of new approved medicines

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Objectives: Through a network evaluation system the Spanish Agency of Medicines and Health Products (AEMPS) in collaboration with the autonomous communities assess the added value of newly approved medicines to decide their financing by the National Health System. The aim was to assess the added value of new medicines and the associated factors.

Methods: An observational retrospective study was carried out on the drug assessment reports published by AEMPS between 2016 and 2017. Information on the efficacy, safety and convenience of medicines, available alternatives and conclusions on added value of new medicines was collected from the published reports. The assessed medicines were classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system.

Results: A total of 92 medicines were evaluated. The most frequent category by diagnosis was MAF-HC for digestive system cancer, onco-hematological disorders, lung cancer, breast and gynecological cancer and urinary system cancer (91% (n = 39), 79% (n = 33); 65% (n = 11); 65% (n = 11) respectively). The OLU category was the highest in nervous system cancer (91%, n = 10). Some drugs had different categories (eg nivolumab (n = 27) with MA-PPF (n = 14), OLU (n = 9) and MAF-HC (n = 4)).

Conclusions: The most frequent category was high-cost medicine authorized in Spain and financed, which is related with the high economic impact of onco (hematological) drugs. Off-label use was the second category, pointing out the absence of drugs for some indications.
neither safety nor convenience were associated with added value.

Conclusions: Only about a third of the new approved medicines had an added value. Factors associated with an added value were the first approved drug for the condition, a higher efficacy either globally or in subgroups of patients and a higher benefit compared to the available alternatives.

CP62  | Assessment and management study of acute pain in hospital services and educational intervention (EDURG17): protocol study

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Objectives: Although acute pain is one of the most common reasons patients visit hospital emergency services, several studies have shown that between 50-70% of patients with acute pain don’t receive adequate medication in the Emergency Room (ER).

The aim is conduct a real-life observational and transversal study on the current pharmacological management of acute pain in the ER of Spanish centers, and evaluating the effectiveness of educational intervention measures on the management of acute pain in the health staff of the hospital ER.

Secondary objectives are intended to describe adequacy of the analgesics use according to recommendations of national guidelines; analyze delay time from admission until treatment is administered, as well as describe the tolerability and safety profile of drugs used to manage the acute pain in the ER.

Methods: 1400 patients attending the 21 participating hospital ERs will be included, presenting acute pain and regardless of whether they are treated or not with some analgesic and at what dose during two periods of one month, separated by a 1 month period of educational intervention (consisting in clinical and informative sessions to all physicians who give assistance in the ER, and distributing therapeutic information bulletins and acute pain management protocols in ER), and a rest period (2 months). A total of 700 patients will be recruited in each of both phases. Design, management, monitoring and analysis of the study will be performed by members of SCReN (Spanish Clinical Research Network).

Results: The study will be carried out throughout end of 2018 and 2019.

Conclusions: This study will provide a global view of pain management in the ER and the utility of the use of educational intervention measures.

CP63  | Use of oxycodone: a descriptive and retrospective study in palliative care

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Objectives: To describe the pattern of oxycodone use in the palliative care unit of a level III hospital.

Methods: We designed a descriptive, observational, retrospective, prescription-indication study. Patients who had been prescribed oxycodone during their admission in the Palliative Care Unit of the “Hospital Universitario Puerta del Mar” during the last four years (2013-17) were included. Main endpoint was the therapeutic indication. The study was approved by the Ethics Committee of Cádiz and classified as “other design” post-authorisation study (EPA-OD) by the AEMPS.

Results: Forty-six patients were included; mean age was 67 years (range: 38-88) and 50% were female. The most frequent reasons of admission were inadequate control of pain (30%), sepsis (13%) and pneumonia (11%). A total of 80% patients (n = 37) were receiving oxycodone previously and the prescription was maintained during admission; the remaining 9 patients were switched to oxycodone during admission due to neurotoxicity (n = 5), insufficient control of pain (n = 3) or excessive sedation (n = 1).

Oxycodone was always prescribed according to the approved therapeutic indication; pain was classified according to its origin in neuropathic pain (n = 39), somatic pain (n = 5) and proctalgia (n = 2) and etiology (oncologic in all patients).

Regarding the use of adjuvant agents, 26 patients were receiving pregabalin, 19 corticosteroids, 8 amitriptyline and one gabapentin. For the treatment of pain, 20% of patients received oxycodone alone, 41% received one adjuvant agent in addition to oxycodone and 39% received two or more adjuvant agents.

No serious adverse events related to oxycodone were detected during the review clinical data.

Conclusions: With the typical limitations of retrospective studies, oxycodone is used in our Palliative Care Unit in the approved therapeutic indication, mainly in the treatment of neuropathic pain and it is usually prescribed in combination with coadjuvant agents with a good tolerance. From this clinical experience, oxycodone is an appropriate choice for oncologic pain.
Observational study to identify treatment guidelines with potent opioids in a geriatric population

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Objectives: Chronic pain is a subjective experience causing impairment and generating both physical and cognitive dependence, and is considered by the WHO as a public health priority. Currently, geriatric treatment is based on the opinion of experts and extrapolation of studies performed in younger population. We consider of the utmost importance to carry on a descriptive study in the daily practice of the geriatric service on University Hospital of Getafe (HUG), considering the lack of evidence in this population for the use of potent opioids (morphine, hydromorphone, methadone, fentanyl, oxycodone (including oxycodone-naloxone), buprenorphine and tapentadol) to observe the pattern of prescription of this III step analgesics (according to the WHO, potent opioids) in the clinical practice.

Methods: Observational prospective study, performed in the HUG geriatric department. Consecutive patients were included for a period of 3 years. All patients were on a potent opioid medication for intense chronic pain of any etiology in a geriatric hospitalized population. Informed consent was signed, and a prospective 3 month follow-up was carried out with the collection of the following variables: EVA, Euro QoL5D5L, Yesavage Depression Scale and any adverse reactions to the opioid treatment.

Results: 474 subjects who were prescribed potent opioids were reviewed; 394 were excluded due to acute pain, palliative symptomatic prescription, previous chronic analgesic treatment or cognitive impairment. 80 potential subjects met the inclusion criteria: 22 decide not to sign the informed consent. 58 subjects were included. We will describe the basal characteristics, type of opioid, cause of prescription, adverse reaction to medication.

Conclusions: In the geriatric population treatment guidelines there is a lot of extrapolation due to an inclusion misrepresentation in most of the clinical trials. Until this population is adequately included in the upcoming evidence studies, the observational study could serve the clinician to collect adequate evidence about the risk-benefit in this population.

Sacubitril/valsartan prescription at the Servei D’Atenció Primària Barcelonès Nord I Maresme

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Objectives: To assess the prescription of Sacubitril/Valsartan (S/V) in Barcelonès Nord i Maresme Primary Care Service (BNM). To assess whether the prescription follows CatSalut guidelines.

Methods: Cross-sectional observational study. Variables are obtained anonymized from Primary Care electronic Health records. We included all BNM patients with S/V active prescription in May 2018. Variables: age, gender, S/V dose, previous or concomitant treatment with angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-II-receptor antagonists (ARAII), heart failure (HF), ejection fraction (EF), glomerular filtration rate (GFR), potassium, systolic blood pressure (SBP), angioedema, hepatic failure. Descriptive analysis.

Results: 170 patients were prescribed with S/V. 26.4% were women. Mean age: 67.1 years (35-89). There was no register of HF in 47 patients (27.6%) and no cardiological diagnosis in 12 patients. There was EF in 96 patients (56.5%) and in 29 patients was >35%. Mean duration of treatment was 176 days (16-564). 43 (25.3%) patients received full doses of S/V (194 mg/day of S). Out of the patients with >3 months treatment, 78 (45.9%) received doses <194 mg. There was no GFR in 84 patients (49.4%) and it was <30 ml/minute in 3 patients. Potassium was registered in 81 patients (47.6%), with correct values. 164 patients (96.5%) had SBP values, <100 mmHg in 12 patients. One patient had a history of angioedema and another had hepatic insufficiency. In 87 patients (51.2%) there was no treatment with ACEI or ARAII in the previous year. In 6 patients ARAII was not withdrawn when starting S/V.

Conclusions:

- We detected different situations of non-adequacy in the indication and / or continuation of the treatment with S/V: no diagnosis of HF, no previous treatment with ACEI / ARAII, EF >35%, GFR <30 ml/min.
- The prescribed maintenance doses are lower than recommended.
- Quality of register in Health records should be improved.
CP66  |  Pharmacological treatment of fibromyalgia in primary health care

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Objectives: Describe the treatment of patients with fibromyalgia (FM) in our area. Describe the sociodemographic and clinical characteristics and health resources used by these patients.

Methods: Cross-sectional descriptive study. Variables were obtained anonymized from Primary Care electronic Health records. We included all patients with a registered diagnosis of FM in Barcelonès Nord i Maresme Primary Health Service which attends 545 768 people. Variables: age, sex, body mass index, comorbidities, treatment and number of visits were collected. Patients not visited in the last year were excluded. A descriptive analysis of these variables was carried out.

Results: We detected 3208 patients with a diagnosis of FM. The prevalence was 0.59%. 109 patients were excluded and rest 3099 patients. 96.7% were women, mean age 58.1 (SD: 11.6) years. The most frequent comorbidities were: dyslipidemia (50%), anxiety (44.6%), obesity (43.3%), depression (36.3%), spine disorder (35.8%) and osteoarthritis (33.48%). 2828 patients (93.1%) had active treatment. 52% (1615) patients took paracetamol of which 25% (405) with codeine. 4.5% (140) potent opiates. 25.7% (796) patients had a SSRIs and 12% (371) duloxetine, 48% (1501) anxiolytics-hypnotics and 17% (528) antiepileptics (9.4% pregabalin, 5.6% gabapentin). 29.2% were treated with Proton Pumps Inhibitors and 17% with statins. The average annual appointments visits with the Primary Care physicians were 8.10.

Conclusions: In our study, the patients with FM present many comorbidities and a high number of treatments and appointments visits to the Primary Care Health Centers. It is necessary to work these aspects with the new FM units.

CP67  |  Acute coronary syndrome in Catalonia: baseline characteristics of patients from a Sidap cohort (Impact Study)

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Objectives: To describe baseline characteristics of patients with a first episode of acute coronary syndrome (ACS) and their pharmacological treatment prescribed for secondary prevention of cardiovascular outcomes [antiplatelets, statins, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB)] after the event.

Methods: Population-based cohort study including all adults with a first episode of ACS between 2009-2016 in Catalan Health Institute hospitals and followed-up in Primary Healthcare (PHC) centres. Patients will be followed-up from the first episode of ACS (index date) to end of follow-up or until a new ACS, ischaemic stroke or death. To assess initiation of drug exposure to the four study groups, maximum time-lag allowed between index date and first drug prescription was 120 days.

The data source was SIDIAP database, containing anonymized information from electronic health records in PHC. The variables captured were baseline clinical characteristics, diagnoses and comorbidities, and drug exposure to co-medication at baseline and first prescriptions of study drugs after index date.

Results: 10 153 patients met inclusion criteria. Their mean age was 65.7 years-old, 68.6% were men and 78.3% were diagnosed with acute myocardial infarction (AMI). The most frequent comorbidities were hypertension (52.6%), dyslipidemia (41.1%) and diabetes (27%). The most common co-medications at baseline were nitrates (32.6%), antidiabetic agents (24.5%) and diuretics (22.7%). After index date, 7227 (71.2%) patients initiated antiplatelets, 6789 (66.9%) statins, 5238 (51.6%) ACEI or ARB, and 2276 (22.4%) did not initiate any treatment.

Conclusions: We describe a large set of patients with ACS in real-world conditions. Most of them were elderly men who had AMI. Patients not initiating treatment after 120 days post-index date might be followed-up by hospital specialists so we cannot capture their prescription data. Further analyses are needed to assess this issue and to estimate adherence and persistence to treatments.

CP68  |  Drug prescribing in older people: assessment of polypharmacy and possible needs of deprescription

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Objectives: There are enormous differences in the prevalence of polypharmacy in the different studies, which may
range between 5-78%. Polypharmacy has been associated with several important adverse consequences. The aim of this work was to determine the prevalence of polypharmacy (chronic use of five or more drugs) and its predictive factors in elderly population.

**Methods:** This was a cross-sectional design. The study population comprised community-dwelling residents over the age of 65 in Málaga. Patients were selected randomly within each healthcare center. Data recorded included sociodemographic characteristics, clinical status, comorbidity (Charlson), functional (Katz Index, Lawton, Pfeiffer, Geriatric Depression Scale, SF-12) and complete information about drugs intake.

**Results:** A total of 3626 prescriptions were indicated to the 582 patients. The mean age was 73.1 years (SD 5.5), and 57.4% were females. The most common diagnoses were bone and joint disorders (75.3%), hypertension (70.9%) and dyslipidemia (51.7%). The median number of medications per patient was 6.8 drugs (SD 4, range 0-23). The prevalence of elderly people exposed to polypharmacy was 68.6%, while 24.7% of the participants usually took >10 drugs. The most widely prescribed ATC groups were C (80.4% of the patients had at least one drug from this group), A (71.6%), N (66.5%) and B (45.4%). Omeprazol and acetaminophen were the two most frequently used drugs, followed by aspirin, simvastatin, metformin, metamizole and enalapril. The risk factors associated with polypharmacy were comorbidity (OR 1.66), female (OR 2), hypertension (OR 3.93), diabetes (OR 1.93), dyslipidemia (OR 3.37), respiratory disease (OR 2.4), osteoarticular disease (OR 1.72) and psychological disorder (OR 2.12).

**Conclusions:** The prevalence of polypharmacy was high, and shows an increase over previous studies in Primary Care. We think that it is important to develop prudent and rational deprescription models.

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**CP69 | Is methylene blue, off-label use, effective in septic shock?**

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**Objectives:** Analyze the experience of using Methylene Blue (MB) for the treatment of Septic Shock in the Service of Intensive Medicine (UIM) of the Hospital University of the Canary Islands (HUC).

**Methods:** Retrospective observational study, whose sample was recruited using a database of the UIM of the HUC. We selected the patients admitted to UIM since 2016 until July 2017 with the diagnosis of septic shock and treated with MB (n = 50 patients). Then we proceeded to the search in that same database, on the one hand, of epidemiological and clinical variables (gender, age, survival-mortality, severity score SOFA, infection focus); and on the other hand, of hemodynamic parameters (mean arterial blood pressure MAP, heart rate) and dosage of MB and vasopressor drugs.

**Results:** The statistical analysis of the variables through the SPSS computer-program, revealed that with the same dose of MB for most of the patients (100 mg), the mortality percentage was 64%. Survivors had less severity respect to non-survivors (SOFA 8 vs 11; P < 0.001) but a similar need for vasopressors, initially; however MB significantly reduced vasopressor (noradrenaline) requirements in survivors respect to non-survivor septic patients (P = 0.024). In addition, the administration of MB significantly increased the MAP from baseline in all: in non-survivor patients, the increase was maximum after 1 hour and it fell to the basal values after 12 hours, and in the survivors the maximum value was reached after 2 hours, but gradually decreased, keeping in hemodynamically acceptable levels after 12 hours; the difference between both groups was statistically significant.

**Conclusions:** In our study a transient elevation of the MAP was observed with a decrease in the requirements of vasopressors in the survivor patients. Well-designed, prospective studies are needed to define the role of MB as treatment of septic shock and the group of patients who could obtain a better response.
Objectives: To compare the cost effectiveness of methoxyflurane (MOF) versus analgesic standard of care (SoC), for treating patients with moderate or severe trauma pain, in Spanish emergency departments.

Methods: InMEDIATE is a phase IIIb, randomized, open label trial designed by Pain Group of SEMES (Spanish Society of Emergency Medicine) and SCReN (Spanish Clinical Research Network), managed by SCReN and funded by Mundipharma Pharmaceuticals S.L. It included health economic evaluations, comparing the cost of pain relief by time, between the groups. To do this, the costs of relieving 1 point the pain score per minute, were calculated per patient: $\text{€PR}_t = \frac{(\text{Total cost } / \text{Pain relief})}{t}$.

The analysis was carried out from the perspective of the National Health System (including drugs, consumables, nursing time and adverse event management). Methoxyflurane cost considered was the UK price (£17.89). Pain relief at time $t$ was calculated as pain intensity $\text{VAS}_0-\text{VAS}_t$.

Results: 310 patients were included. ITT population: MOF = 156; SoC = 149. SoC treatments were mainly iv opioids. Patients suffered severe pain at inclusion (median $\text{VAS}_0$ = 7.5). MOF demonstrated a significantly faster speed of action: time to first pain relief (median $[\text{IQR}])$ MOF: 3.2 minutes $[1.8-7.4]$ vs SoC: 10 minutes $[5.7-14.6]$ $P < 0.001$, and higher pain relief ($P < 0.001$) at all evaluated time points. There were no significant $\text{€PR}_t$ differences between groups at different point times. The $\text{€PR}_t$ AUC$_{0-20}$ min of MOF (cost of relieving pain score/minute, during the first 20 minutes) was 53% lower than SoC $P < 0.001$.

Conclusions: This trial demonstrates that MOF is cost-effective compared to SoC for emergency relief of trauma pain in patients attending Spanish Emergency departments. It occurs during the analyzed first 20 minutes, despite the difference among drug prices, probably due to MOF faster speed of action and greater pain relief.

Objectives: The study is designed to gather data that allow us to create a new predictive clinical index of VTE in patients undergoing anticancer treatment and to validate the Khorana score in the Spanish and Portuguese population.

Methods: The CARTAGO project is a prospective observational Iberian multicentre study. Tumors with an incidence rate of VTE greater than 10 events per thousand people per year will be selected (1). The inclusion of each type of cancer will be stratified according the cancer statistics in Spain (2). In addition, cancers with a frequency lower than 1.5% of all cancers will not be included(2). The protocol was approved by the ethic committee of each hospital.

An incidence rate of VTE expected is approximately 6% during the six months of follow-up. A sample size of 3000 patients is required by Monte Carlo simulation considering a range of effect sizes measured as HR between 1.2 and 7.4. For the adjustment of the predictive model, a survival analysis will be performed by cox regression with time-dependent variables in which the response variable will be the time to the thrombotic event. We will value the construction of a new model for predicting the risk of VTE. Variable selection will be performed by means of penalized regression methods such as LASSO or Elastic Net.

The final model will be estimated by means of a time-dependent cox regression analysis. Validation and calibration of the model will be assessed using 1000 bootstrap iterations.

Results: The results are expected for the second quarter of 2019.


CP72 | Clinical impact of moderate and several potential drug-drug interactions in medical inpatients: cohort study

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Objectives: The drug-drug interactions (DDIs) are a problem that has been associated with high morbidity, mortality, and healthcare cost, especially in vulnerable population, such as inpatients. However, the studies that support these conclusions are scarce and show methodological problems, which makes it difficult to extrapolate the results obtained. For this reason, we believe that is necessary to determine the association between potential DDIs on severe clinical outcomes in inpatients.

Methods: We conducted a prospective and concurrent cohort study. The target populations were medical non-critical and critical inpatients ≥18 years. We evaluated the presence of moderate and severe potential DDIs and its association with mortality during hospitalization or until 30 days after hospital discharge; length of hospital stay and hospital readmissions within two weeks after hospital discharge. Control of confounding factors was performed.

Results: We identified 1170 potential DDI. We found that potential DDI was related to a longer hospital stay, where patients with at least one potential DDI had a higher average hospital stay than those without potential DDI (8.7 days vs 5.4 days, P = 0.003). We did not find impact on other clinical outcomes. The results did not change when adjusted for age, polypharmacy and comorbidity.

Conclusions: We found a high prevalence of DDI, which may increase the hospital length of stay. This could be increase the morbidity and healthcare cost.

CP73 | Psychotropic drug consumption in European children

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Objectives: to describe the use of psychotropic drugs in children ≤18 years from Catalonia, Denmark, Sweden and Norway in the last decade.

Methods: descriptive observational study with population under 19 years old with at least one dispensing of a psychotropic drug (antiepileptic’s, antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, antidepressants, psychostimulants) from 2007-2017. Nordic data have been retrieved from their dispensing database covering 99% of their population, and Catalonia data from the Information System for Research in Primary Care (SIDIAP) database covering population attended at the Catalan Health Institute (ICS). The prevalence of psychotropic drug use is determined during each year by age and sex groups; calculating psychotropic users 1000 children per year according to the pharmacological subgroup by ATC codes.

Results: psychotropic consumption has increased in the last decade in the Nordic countries (Denmark 36%, Norway 17%, Sweden 174%) meanwhile in Catalonia has decreased 16%. In 2017 Sweden shows the highest consumption (77.1 users/1000 children) and Catalonia the lowest (21.3 users /1000 children).

The most consumed psychotropic drugs are the psychostimulants in all countries followed by the hypnotics/sedatives in the Nordic countries. In all countries the psychostimulants are most consumed by boys over 10 years, and antidepressants are most consumed by girls over 15 years. The consumption pattern of anxiolytics and hypnotics/sedatives is variable among countries. Antipsychotic consumption has increased during the last decade in all countries and with children age.

Conclusions: The Nordic countries show higher psychotropic drug consumption in children ≤18 years from Catalonia, Denmark, Sweden and Norway in the last decade.
Objectives: The Antimicrobial Stewardship Program (ASP/PROA in Spain) of the Hospital Universitario de Canarias was created in 2015. Among its objectives is the improvement of clinical results of patients with infections, minimization of adverse effects associated with the use of antibiotics (resistances), safe-guarding cost-effective treatments, and compliance with the AEMPS’s and WHO’s plans. It also provides training for health professionals. APS has been adapted to the characteristics of the hospital, acting on bacteremia, and monitoring annual incidence of isolated multi-resistant germs, and antibiotics consumption.

Methods: Analysis of ASP activity, focusing mainly on intervention strategies against bacteremias occurred in our hospital from the start of ASP activity until December 2017.

Results: We analyzed 1431 events of bacteremia, of which 892 episodes (63%) were intervened. With regard to antibiotic intervention, duration of antimicrobial treatment (80%) and adequacy of the antibiotic (73%) -including de-escalation (78%), equal or greater spectrum (18%), dose optimization (4%), intravenous to oral conversion (35%), initiation (6%) and discontinuation of treatment (4%) - were established. The number of non-surgical patients was 539 (37%). The causes of non-intervention (279): culture and susceptibility results demonstrated a non-pathogen (11%), empirical therapy was considered appropriate (23%), death (2.5%), and other (16%). Compliance of physicians in the different hospital services with the Infectious Disease specialist’s recommendations on antibiotics use and length of treatment (84 and 80% respectively), was determined by the Clinical Pharmacologist.

Conclusions: Since creation of ASP, duration and adequacy of the antibiotic treatment have been optimized, achieving de-escalation in a high proportion of patients. The aim is to change the culture of prescription, adapting antimicrobial use and reducing resistance with these measures, among others. Future studies should evaluate the impact on the microbiological map in our geographic area.

Objectives: To reduce prescription of not suitable treatments in patients with ACD.

Methods: Prescription-indication drugs use study (before/after), oriented to deprescribing not suitable treatments in ACD patients.

In 2016 and 2017, two different interventions were carried out to improve the adequacy of treatment in patients ACD in a Primary Care Service (“SAP Baix Llobregat Centre”; 423 369 inhabitants with 19 primary care Centers [PCC]). The chronicity team, together with local medication consultants, extracted data from ACD patients, who have in their prescriptions some drugs that are considered not suitable for their conditions statins, bisphosphonates or pentoxifylline..).

In November 2016, the information of the patient with any incidence of not suitable prescription was send by e-mail to the director of every PCC. A letter with deprescribing recommendations was attached also into the e-mail. In a second phase, in March 2017, a new extraction with the same characteristics was extracted and sent, directly to the doctor who attend the patient, with a specific recommendation of drugs deprescribing. After each intervention, the incidences of not suitable prescriptions were reanalyzed.

Results: In the first intervention, the number of ACD patients with some incidence was 195 patients. Four months after the intervention, 26.7% of the patients died (n = 52), the incidences with any drug (n = 157) of the rest of the patients (n = 143), were reduced in 2.6% after intervention.

In the second intervention, the total number of patients with incidences was 200 patients. 19.5% of the patients died (n = 39), and the incidence with any drug (n = 180) of the rest of the patients (n = 161) was reduced in 1.1% after intervention.

Conclusions: Neither the strategy to improve non adequate use of drugs in ACD patients directed to the director of the PCC nor directed to the doctor with concrete recommendations, were effective.
**CP76 | Intervention to improve the safety in the use of non-insulin oral antidiabetic drugs (NIOAD) in patients with type II diabetes mellitus in a primary care trust (PCT)**

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**Objectives:** Intervention to improve the safety in the use of non-insulin oral antidiabetic drugs (NIOAD) in patients with type II diabetes mellitus in a primary care trust (PCT).

**Methods:** Drug use study (before/after), to improve safety of NIOAD, in diabetes type II patients, in PCT Costa de Ponent (1 324 342 inhabitants, 56 primary care centers [PCC]).

In December 2017, security incidences in use of NIOAD were analyzed. The incidences were related to: (1) contraindications or precautions according to technical specifications of ADONIs, according to patient’s age, renal hepatic or cardiac failure, pancreatitis, inflammatory bowel disease, amputations…), (2) contraindications with concomitant treatments (repaglinide and gemfibrozil), or (3) metabolic excessive treatment; patients ≥80 years of age, or in situations of fragility and / or advanced chronic disease and values of HBA1c <6.5.

Between January and April of 2018, the study was presented in the different PCC, and each family doctor received a list with different safety incidences or treatments considered excessive in attended patients. In May 2018, the impact of the intervention was analyzed.

**Results:** At the beginning there were 3351 patients, with some security incidences related to NIOAD. The average age of population was 72 years old and 48.1% were women. After the intervention, 96 patients died and 14 patients moved to another area. Analyzing the data of patients who have complete information of the prescription drugs (n = 3.241), there was a 26.5% reduction of patients with a security incidence related to NIOAD, and a 28.1% reduction of the number of incidences. Contraindicated incidences were reduced in 52, 2% (from n = 520 to n = 248), and precautions incidences were reduced in 23.9% (from n = 3.041 to n = 2.314).

**Conclusions:** Interventions implemented in PCC to improve security incidences with the use of NIOAD, improves the safety with the use of these drugs.

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**CP77 | Quasi-experimental study of an intervention on the pharmacological management of non-oncological chronic pain**

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**Objectives:** To assess the impact of an intervention to adapt the treatment with opioids and transdermal lidocaine in patients with Non-Oncological Chronic Pain.

**Methods:** A quasi-experimental study before/after a formative intervention in Primary Care physicians of the Direcció d’Atenció Primària Metropolitana Nord (Barcelona) and an informative intervention about their non-oncological patients with one of these treatments: fentanyl citrate; potent opioids and ≥ 2 anxiolytics-hypnotics chronically; potent and weak opioid patterns; transdermal lidocaine out of indication. From the computerized clinical history, 2 anonymized extractions were performed before and after the intervention (July-November 2017).

Main variable: variation in the number of patients with some incidence, before and after the intervention. Descriptive analysis and calculation of 95% confidence intervals (CI) for proportions with bilateral contrast were done. A reduction ≥ 15% was considered statistically significant.

**Results:** Incidence reductions in the initial cohort were: 37.29% (95% CI 29.08-46.29) for fentanyl citrate, 40.96% (95% CI 36.34-45.76) for potent opioids and ≥ 2 anxiolytics-hypnotics chronically; potent and weak opioid patterns; transdermal lidocaine out of indication. From the computerized clinical history, 2 anonymized extractions were performed before and after the intervention (July-November 2017).

In the data extraction of December, the appearance of new patients with these incidences was observed, although the number of these patients was lower than that of those who withdrew the medication.

**Conclusions:** The reduction in the number of patients reported initially has been higher than the new cases included in the final cut. The intervention has been effective but it is necessary to maintain it over time due to the appearance of new cases.
SECTION: E. CLINICAL PHARMACOLOGY
TEACHING. OTHER ISSUES

CP78 | Bioethics and autonomy in the treatment compliance of chronic pain
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1UMH; 2ISABIAL; 3HGUA, Alicante, Spain

Objectives: To analyze the extent to which the doctor-patient relationship and the level of understanding of the information provided, influences the decision to accept or not the opioid treatment and its subsequent opioid treatment compliance.

Methods: A prospective observational study was developed in ambulatory patients from the Pain Unit of the General University Hospital of Alicante (HGUA). Subsequently, a descriptive analysis of the data and a statistical analysis with a multiple linear regression and a Chi square test with R 3.2.4 were carried out. Clinical Research Ethics Committee approved the study.

Results: A total of 69 patients participated (74% women, 62 years on average, 72% retired, pain intensity 6 ± 3 cm, 10 ± 11 years of pain evolution). Of them, 81% with opioids (average dose 95 ± 88 mg / day) that come 35% to 10 ± 11 years of pain evolution. Of them, 81% with opioids and it is associated with high mortality. MALA

Conclusions: Lactic acidosis is the major toxicity of metformin and it is associated with high mortality. MALA should be suspected in patients receiving correct dose of metformin who gets affected by acute circumstances such as renal insufficiency, liver disease, sepsis and dehydration and also in overdose. Immediate notification of critical values, high plasma lactate and low serum pH, from laboratory is important to establish the diagnosis as soon as possible. Metformin serum concentration higher than 5 mg/l leads to definite confirmation of MALA.

CP80 | About a case of acetaminophen accidental toxicity in nursing infant
Maria Gabriela Vaca Recalde; Noelia Vega Gil; Sandra Llorente Pelayo; Ana Orizaola Ingelmo; Pedro Daniel Ortiz Petrosino; Rita Nogueiras Álvarez; Iván Mazón Maraña; Nuria Sánchez Avello; Blanca Sánchez Santiago
Hospital Universitario Marqués de Valdecilla, Santander, Spain

Objectives: We present a case of acetaminophen toxicity to discuss the not uncommon occurrence of difficulties to recognize children at increased risk in whom standard acetaminophen doses were administered.

Methods: A two-month-old female infant was attended at our hospital due to bad general status, low grade fever and weight loss. Hepatotoxicity and impaired renal function were seen and patient was admitted to neonatal intensive

CP79 | Metformin-associated lactic acidosis retrospective review
Noelia Vega Gil; Sonia Pérez San Martín; María Gabriela Vaca Recalde; Rita Nogueiras Álvarez; Blanca Sánchez Santiago; Pedro Ortiz Petrosino; Iván Mazón Maraña; Nuria Sánchez Avello
Hospital Universitario Marqués de Valdecilla, Santander, Spain

Objectives: In order to study the occurrence of metformin-associated lactic acidosis (MALA) in our hospital, a retrospective review of the cases where metformin serum concentration was measured and found to be higher than upper limit of therapeutic range was performed.

Methods: Metformin concentration serum level database was reviewed and those patients whose concentration was upper the limit of 5 mg/L (value associated with MALA) were selected. A review of clinical history was done especially attending to blood pH, lactate, serum creatinine, renal clearance and comorbidity factors. Clinical situation, evolution and response to treatment were reviewed as well. To determine metformin serum concentration, Liquid Chromatography tandem-Mass Spectrometry (LC-MS/MS) was used.

Results: From December 2016 to May 2018 eleven patients were selected. They were 4 male, 7 female and median age at the time of diagnosis was 64. One case was caused by self-harm deliberate overdose but the rest occurred secondarily to renal insufficiency due to dehydration, infection, sepsis or liver disease. Metformin serum level was 52.40 ± 18.49 mg/l (mean ± SD) with minimum value of 25.11 mg/l and maximum 86.90 mg/l. Mean serum creatinine: 9.90 ± 3.21 mg/dl (value from self-overdosed patient censored). Mean blood pH: 6.89 ± 0.21 and mean blood lactate: 120.3 ± 31.2 mg/dl (normal range: 4.5-14.0). All patients required intensive care. Three out of 11 patients died.

Conclusions: Lactic acidosis is the major toxicity of metformin and it is associated with high mortality. MALA should be suspected in patients receiving correct dose of metformin who gets affected by acute circumstances such as renal insufficiency, liver disease, sepsis and dehydration and also in overdose. Immediate notification of critical values, high plasma lactate and low serum pH, from laboratory is important to establish the diagnosis as soon as possible. Metformin serum concentration higher than 5 mg/l leads to definite confirmation of MALA.
care unit. Differential diagnosis focused in metabolic disease and infection. Parents were interviewed about possibility of intoxication but response and drugs in urine test were both negative. Despite no cause was identified at that moment, clinical situation was improving with symptomatic and supportive care. On day 3 parents informed about a single dose of acetaminophen (48 mg) which seemed to be appropriate.

**Results:** Acetaminophen serum concentration was determined at Clinical Pharmacology laboratory by using particle-enhanced turbidimetric-immunoassay technology and resulted to be 15.8 mg/l. Although this was performed on day 3, a blood sample obtained when patient was firstly attended at hospital was used. Acetaminophen exposure had occurred 58 hours before blood sampling, so no Rumack-Matthew’s nomogram could be applied and no N-acetylcysteine antidote (NAC) was administered. Clinical response to supportive care and weight gain were positive. Liver function abnormalities got resolved and prerenal insufficiency as well. Baby was discharged on day 19.

**Conclusions:** Risk of developing toxic reactions to acetaminophen is lower in children, but this toxicity is not just attributable to inappropriate dosing. In children at increased risk of toxicity, standard doses cause toxic reactions, as it occurred in our patient. It is important to recognize this cases so as to determine acetaminophen serum level and administer NAC on time. Our patient had a positive outcome but it is important to note that there are developmental differences in hepatic metabolism that may affect hepatotoxicity in infant and young children.

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**CP81 | Preferences about drugs and therapeutics information and interest in new tools: an opinion survey among hospital physicians**

Johan Humberto Ayala Oliveros; Roser Llop Rius; Consuelo Pedrós Cholvi; Pilar Hereu Boher

_Hospital Universitari de Bellvitge, Barcelona, Spain_

**Objectives:** To assess the frequency of consultation of news about drugs and therapeutics available on Clinical Pharmacology Department section of Hospital Universitari de Bellvitge intranet by physicians, their main search methods on therapeutic information, and their potential interest in new drug information products.

**Methods:** An opinion poll among physicians from 12 different medical services was conducted between October and December 2017. The following information was collected: (1) frequency of use of the drugs and therapeutics news section on the intranet; (2) most frequently used search methods about information on drugs and therapeutics; and (3) potential interest in new products, tools and ways of getting information.

**Results:** Among 185 physicians, 174 (94%) answered the survey. Sixty eight percent do not usually visit the news section about drugs and therapeutics on the intranet. Physicians from Psychiatry and Infectious Diseases departments showed the highest and the lowest frequency of use, respectively. The search methods most frequently used were Google and websites of regulatory agencies (30% of physicians each), followed by PubMed (24%). Only 35% of physicians stated to have a Twitter account. Most respondents (74%) showed potential interest in new tools and ways of getting information on drugs and therapeutics.

**Conclusions:** There is an infrequent use of information resources about drugs and therapeutics offered by the Clinical Pharmacology Department through the hospital intranet. Physicians mainly use Google and websites of regulatory agencies. In accordance with the interest that they have manifested, the convenience of offering new tools and ways of disseminating information about medicines and therapeutics should be considered.

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**CP82 | Use of clinical trials (CT) in oncology drugs (OD) and utility of therapeutic positioning reports (IPTs) in taking a treatment decision**

Irene García García; Amelia Rodriguez Mariblanca; Lucía Martínez De Soto; Lucía Díaz García; Jaime Monserrat Villatoro; Javier Queiruga Parada; Alberto Borobia Pérez; Antonio Carcas Sansuán

_Hospital Universitario La Paz, Madrid, Spain_

**Objectives:** IPTs were introduced in May 2013. Their main objective is to evaluate the added therapeutic value of new medical products and to inform about its relative positioning in the treatment of the disease of interest. Our objective was to evaluate the quality of CT leading to OD marketing approval and to assess the utility of IPTs recommendations.

**Methods:** Descriptive study based on information from IPTs, publicly available in the Spanish Agency of Medicines and Medical Devices website (until 14/06/2018). All IPTs concerning OD were reviewed focusing on pivotal studies characteristics, primary endpoints(PE) evaluated and recommendations made in the report. Recommendations were classified in four categories: DEFINED: indication and positioning is well described; ALTERNATIVE: alternative treatment recommended; EFFICIENCY: decision must be made based on economic criteria; PERSONALISE: clinicians decide the suitable patients to treat.
Results: Fifty-nine IPTs for OD were available. The indication was mostly advanced or metastatic disease. A least two positive, adequate CT has been historically the gold standard to provide evidence to support the approval of new drugs. However, we found only 6 out of 59 OD approved based on at least two phase-III CT with global survival(SG) as PE. Twenty-four OD were approved with only one phase-III CT which PE was SG, 4 of these had also a phase-II study. We found 30 OD based on one phase-III study with progression free survival(SLP) as PE. Three OD were authorized based on only one phase-II clinical trial. Their PE was SLP. IPT conclusions were mostly classified as EFFICIENCY (24) and PERSONALISE (13). Twenty-two conclusions were categorized as DEFINED (11) and ALTERNATIVE (11).

Conclusions: Only 6.74% of OD studies achieved criteria for providing substantial evidence to support regulatory approval. 62.7% of IPTs recommendations were considered of low utility in positioning of the new drug into the standard treatment protocols.

Use of a commercial film to teach the pharmacovigilance system: La fille de Brest

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Objectives: Popular movies are increasingly used as a teaching method in many college disciplines. We have described previously the use of movies to teach pharmacology and clinical pharmacology. We used a French popular movie entitled “La fille de Brest”, based on real events, that reports the fight between a doctor and the French pharmaceutical company Servier and the Health Product Safety Agency, to induce the withdrawal of the drug Mediator® (Benfluorex, 150 mg). The objective was to illustrate the pharmacovigilance system.

Methods: The movie “La Fille de Brest” (2017, directed by E. Bercot) is based in the book “Médiateur 150 mg: Combien de morts?” (I. Franchon, 2010). It explain the case of the adverse effects induced by the substance benfluorex in France that begin in 2006 and finished with the withdrawal of the drug in 2009. The movie was analyzed by two independent evaluators in order to find different aspects related to its possible use for teaching some of the multiple aspects of the pharmacovigilance system.

Results: The film includes scenes about the appearance of the clinical cases, the use of yellow card to report adverse events, the relevance of signals for drug safety, the role of the Safety Committee in the French Medicines Agency, the development of confirmatory studies (case-control), the role of conflict of interest, the relevance of press media in health decisions, and the differences between Medicines Agencies in withdrawal drugs. We prepared a list of teaching objectives, questions to guide the discussion after viewing the movie in a seminar, and the evaluation.

Conclusions: Our analysis concluded that “La fille de Brest” could be a useful tool to describe all the processes involved in the pharmacovigilance system (from clinical case signal to the withdrawal of the drug from the market). We propose its use in teaching these topics in clinical pharmacology courses.
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