# 6th Pharmacovigilance Congress

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## Posters

*Pharmacovigilance Congress 2016*

Armen S Galstyan, J Pharmacovigil 2016, 4:5 (Suppl)
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## Derivatives of 1,2,4-triazoles: Synthesis and study of biological activity

**Armen S Galstyan**
Yerevan State University, Armenia

One of the most interesting classes of organic compounds such as nitrogen, oxygen, and sulfur-containing heterocycles have a wide range of practical use. In particular 1,2,4-triazol-ring included in the structures of different biologically active molecules, are used as drugs with broad spectrum action, e.g. antimicrobial (Fluconazole, Itraconazole), anticancer (Vorozole, Letrozole, Anastrozole), and some derivatives have antibacterial, antifungal, antitumour, anti-inflammatory, antitubercular, hypoglycemic, antidepressant, anticonvulsant, antiviral and analgesic activity. This work presents some synthetic possibilities of 3,4-disubstituted-5-mercapto-1,2,4-triazoles to obtain new potentially biologically active compounds. For functionalization of tria¬zoles, we carried out the cyanoethylation and (methoxy¬car¬bonyl)ethylation reactions in the reaction conditions. The basic and acid hydrolysis of the resulted compounds was realized, which led to the corresponding 3-heterylsubstituted propionic acids. Hydrazinolysis of synthesized esters of hydrazides were obtained. The last are given in 1,3,4-oxadiazoles and pyrazoles according to known methods. Sulfur-substituted 1,2,4-triazoles derivatives may also be interesting in biological viewpoint. This would enable the biological activities of free and substituted thiols to be compared. Therefore, 1,2,4-triazoles were alkylated by various aralkyl halides. In order to obtain the derivatives of thiazolo[2,3-c]-1,2,4-triazoles studied the bromination reaction of 4-allyl and 4-methallyl substituted triazoles. Preliminarily tests of compounds S-derivatives for antioxidant activity revealed that the latter exerts stabilizing effect on red blood cell membranes. Screening of some compounds revealed that they exhibit feebly marked antibacterial and anti-yeast activity. But 3-benzyl-1-(2-(5-mercapto-1,3,4-oxadiazol-2-yl)ethyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione could inhibit the growth of Gram positive bacteria.

### Biography

Armen S Galstyan has completed his PhD from Supreme Certifying Commission of the Republic of Armenia and Postdoctoral studies from Yerevan State University. He is Head of Educational Laboratory, Department of Organic Chemistry, YSU, and Research Associate of Research Laboratory, "Chemistry of N-, S-, O-containing Heterocyclic Compounds". He has published more than 45 international thesis, patents and articles in the reputed journals.

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## New syntheses in the field of τ-lactones and biological studies of the obtained compounds

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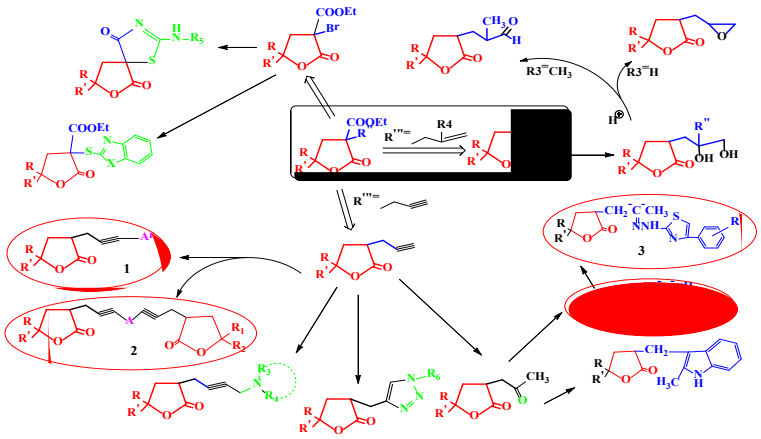
A wide range of biological action and prevalence of lactone-containing compounds in the nature become attractive objects for research by both specialists in fine organic synthesis and pharmacologists. There are numerous drugs used in medicine that contain active aglycones derivatives of γ-lactones. The relevance of research in the field of γ-lactones is confirmed by numerous recent publications. In continuation of our research in this field, we have developed a number of methods for the synthesis of new, earlier not described in literature lactone-containing compounds that can be of certain practical interest. Below there is a graphical scheme of our research. Screening of compounds 1,2 revealed that they displayed inhibitory activity in relation to major phosphatases. It is shown that the inhibitory activity of the main part of studied compounds exceeded similar properties of the known inhibitors levamisil and L-phenylalanine by 17-80 times. Compounds 3 are of certain interest. Their studies have shown that representatives of this class have mainly antibacterial properties were used Gram-positive staphylococci (209P, 93) and gram-negative rods (Sh. Flexner 6858, E coli 0-55), all compounds had moderate anti¬bacterial activity. Screening has revealed antimutagenic properties in a series of γ-lactones for the first time (compounds 3, 4). The experiments were carried out on *Salmonella tiphimurium* TA-100. It was established that with these compounds the number of revertants decreased by 55-60% and mutagenicity factor w as 2.58-2.7. The same compounds exhibited algicidal activity against filamentous green algae Cladophora. The mentioned compounds in 1 mg/ml concentration destroy cells for 51-60% against 14% of the control preparation monuron. Undoubtedly, compounds 3, 4 can be used in solution of some ecological problems.



### Biography

Tariel V Ghochikyan has completed his Doctor of Sciences degree from Supreme Certifying Commission of the Republic of Armenia (Yerevan State University). He is Dean of the Department of Pharmacology and Chemistry, YSU. He is Supervisor and Master Researcher of Research Laboratory, "Chemistry of N-,S-,O-containing heterocyclic compounds". He has published more than 225 articles, international thesis and patents in the reputed journals. He is the member of the Council of YSU, member of special soviet unions. He is an Editorial Board Member of *Chemical Journal of Armenia*, and also for the proceedings of YSU Chemical and Biological Sciences.

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## Radical scavenging activity and phytochemical constituent of *Tulipa Systola Stapf*

**Mohammed Farhad Ibrahim**
University of Salahaddin, Iraq

**Introduction**: People living on the mountains of the Kurdistan region in Northern Iraq use large amount of herbs for local traditional medicine. Among them, *T. systola*, which grows under and between rocks, is very popular as a herbal anti-inflammatory remedy and pain-relief; two or three fresh bulbs eaten by the patient particularly during inflammation and birth pain. *Tulipa systola* Stapf. was collected in April 2014 on the Korek Mountains in Rewanduz-Erbil/Kurdistan region. The materials were identified and classified from Education Salahaddin University Herbarium (ESUH) by Dr. Abdullah Sh. Sardar, at the University of Salahaddin, Erbil-Iraq. A voucher specimen was deposited with the accession number (7201).

**Experimental**: *Tulipa systola* roots, leaves and flowers (100 g each) were separately defatted with petroleum ether (500 mL), in an ultra-sonic bath for 30 min, then macerated for 3h under continuous stirring at room temperature. The procedure was repeated three times for each part. Defatted roots, leaves and flowers were subsequently separately extracted with ethanol (500 mL) in an ultra-sonic bath for 30 min, and then macerated for 3h under continuous stirring at room temperature. The procedure was repeated three times for each part. The mixtures were then filtered and the solvent was removed under "vacuum" in a rotary evaporator to afford crude ethanol extracts: TR from roots, TL from leaves and TF from flowers, respectively. The concentrated extract TR, TL and TL (1 g), each extract separately was chromatographed over (MPLC (Isolera) RC18, Methanol/Water; (20:80 – 100% methanol) gradient to afford different fractions. From further purification of these fractions, some pure bioactive compounds isolated and then identified by spectroscopic; IR, UV, NMR and MS analysis as, TRD2: (+) 1-O-feruloyl-3-O-p-coumaroyl-glycerol and TRB2: (+) 6-tuliposide A from Roots, TLW5 and F3: (-) Kaempferol-3-O-rutinoside from both Leaves and Flowers part.

**Results**: This is the first report about phytochemical constituent of *Tulipa sytola* Stapf. growing in Kurdistan region Iraq. The radical scavenging and antioxidant activity of the isolated compounds were evaluated on four tests: DPPH free radical scavenging activity, ferrous ion-chelating power test, total antioxidant activity, hydrogen peroxide scavenging activity, which were carried out as described in the literatures. Compared to the reference ascorbic acid the IC50 values of the most active compounds were: (DPPH; IC50, Ascorbic acid 55 µg/ml > F3 65.4 µg/ml > TRD2 77.1 µg/ml > TRB2 135.5 µg/ml), (hydrogen peroxide scavenging; IC50, F3 36.91 µg/ml > Ascorbic acid 38.37 µg/ml > TRD2 40.83 µg/ml), (TAOC; IC50, Ascorbic acid 57.53 µg/ml > TRD2 81.99 µg/ml > F3 121.08 µg/ml). The significant antioxidant and antiradical activities determined for the different compounds give scientific support to the traditional use of the plant by the Kurdish people as a popular anti-inflammatory remedy and pain-relief and a great subtend to become a starting point for *in vivo* investigation in the next steps.

**Conclusions**: To the best of our knowledge, the optical active isomer of compound TRD2 (+) 1-O-feruloyl-3-O-pcoumaroyl-glycerol for the first time had been isolated from *Tulipa systola* roots. The study of the variety of secondary metabolites occurring in *T. systola* as a potential source for natural bioactive chemicals, as well as their precise antioxidant mechanisms, is therefore worthy of being carried out, and it will be reported in due time.

### Biography

Mohammed Farhad Ibrahim is a third year PhD student in Natural Product Chemistry and Drug Discovery from medicinal plants. He was awarded MSc degree at University of Pavia, Italy. He worked as Supervisor in the department of Cosmetic and Pharmaceutical Products at Xenofarma company.

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## Prenatal exposure to alcohol impairs the long term integration of GABA interneurons and the proteolytic endothelial activity in mouse neonates

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During brain development, the NMDA receptor exerts trophic activities and is required for a correct integration of GABAergic interneurons. The literature informs us that a prenatal alcohol exposure impacts the glutamatergic transmission. It is now established that brain vessels are involved in the migration of GABAergic neurons and we recently showed that endothelial cells express NMDA receptors. In the present study, we hypothesized that in utero alcohol exposure might impact the cortical integration of GABAergic neurons via an alteration of the endothelial cell activity. Using Gad67-GFP mice, we investigated the effects of a prenatal alcohol exposure on the survival of GABAergic precursors, the activation of endothelial MMPs and tPA and the long term integration of GABAergic neurons in the neocortex. Treatment of cortical slices from E15 fetuses with ethanol revealed no significant modification of the apoptotic death. In contrast, both in situ and gel zymographies showed that alcohol markedly reduced the proteolytic activities of MMP9 and tPA in cortical microvessels. These effects were mimicked by the NMDA antagonist MK801. A long term follow-up of the GABAergic interneuron population revealed that a prenatal alcohol exposure increased the density of cortical GABAergic neurons and GFP expression levels but decreased the density of primary dendrites per neuron. Altogether, these findings support that a prenatal alcohol exposition disturbs the activity of vascular matrix proteases and the long term integration of GAD67-GFP interneurons. They raised the question of long term effects of molecules with NMDA antagonist properties such as anesthetics.

### Biography

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## Prospective observational study for oxaliplatin induced hypersensitivity: Experience in a single institute during 2 years

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**Background**: Oxaliplatin-related hypersensitivity reactions (HSR) are well-known, raising a dilemma for use of critical drug in cancer patients for fear of inducing severe reactions and even fatal, anaphylactic reactions. However, the prevalence varies and data on the incubation period for sensitization and grade of severity have not been reported prospectively.

**Methods**: We performed prospective, observational study with 745 patients treated with oxaliplatin-based chemotherapy between March 2003 and January 2015 in Seoul National University Cancer Institute. Oxaliplatin HSR was assessed by structured telephone interview. We examined prior exposure to oxaliplatin, incubation period, severity of HSR and premedication treatments.

**Results**: During the period, a total of 745 patients were enrolled, and 148 (18.7%) HSR events were reported. Depending on patients with prior exposure to oxaliplatin, 40.3% of previous exposed group exhibited HSR (48/119), significant higher than non-exposed group. (15.9%, (100/526), $p < 0.0001$, by Fisher's exact test). The average median cycle of the HSR was 3.31 in previous exposed group. In contrast, previous non-exposed group experienced HSR at cycle 4.53 ($p<0.0001$). By National Cancer Institute criteria (version 3.0), the severity of HSR was higher in patients with a previous history of oxaliplatin than in patients without previous exposure. (Grade 2.8±0.1 (Gr 1: 8.3%, Gr 2: 25.0%, Gr 3: 47.9% and Gr 4: 18.8%) vs. Grade 2.3±0.1 (Gr 1: 14%, Gr 2: 42%, Gr 3: 41% and Gr 4: 2%), respectively ($p=0.005$).

**Conclusions**: In this prospective study, we observed that patients with any prior exposure to oxaliplatin experienced earlier onset and more severe HSR with a higher frequency, despite of premedication. We concluded that patients with history of exposure to oxaliplatin HSR in early cycle with severe allergic reactions can occur and is needed for tailored modification such as desensitization.

### Biography

Kyoung Hee Sohn received a Bachelor's degree from Kyungpook University School of Medicine. She is currently pursuing her Specialization in Clinical Pharmacology and Therapeutics at the Seoul National University Hospital. She has published some papers in SCI journals in the field of allergy and pharmacovigillance and is speaker in several global conferences.

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## Pharmacovigilance and compliance of drugs labeling information with the 2015 FDA Lactation Guidelines

**Faten Sabbagh**
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This study was conducted to evaluate published and manufacturer labeling information (PI) for commonly prescribed drugs in the USA, and to examine compliance with the new 2015 FDA labeling guidelines. Data were also compared to the authors' previously published information on the development of the first clinical classification of drugs used during lactation (FG-LA). Of the top 200 drugs prescribed in 2015, 85% included a lactation section but information was limited and not in compliance with all elements of FDA guidelines. Only 5% included risk versus benefits section, 54.5% were excreted into breast milk or included data on milk-plasma ratio. Utilizing FG-LA clinical classification, 53.5% were clinically compatible with lactation but 19.5% caused mild to moderate adverse effects on infants, and 1.5% caused mild to moderate adverse effects on the mothers. A total of 23.5% were classified as incompatible with lactation, secretion of 11.5% was unknown, 6.5% caused mild to moderate adverse effects on infants and 1.5% caused mild to moderate adverse effects on the mothers. A total of 23% were classified as unknown with compatibility and no data on adverse effects were reported on infants or mothers. A total of 25.5% caused adverse effects on infants and 3% had adverse effects on the lactating mothers. Several conflicts existed between data in the PI and the literature addressing secretion or concentrations in breast milk. A firmer deadline is recommended by the FDA to drug manufacturers to update PI data in order to enhance patient safety and therapeutic outcomes.

### Biography

Faten Sabbagh is a PharmD Candidate at South College School of Pharmacy in Knoxville, Tennessee, USA. Her undergraduate study included Biological Sciences at the University of Michigan-Dearborn and Henry Ford College. He has been in the practice of pharmacy since 2010 with certifications in Medication Therapy Management, AHS-BLS, Immunization Delivery, Smoking Cessation, and Diabetes. Her areas of interest are Pharmacokinetics, Pharmacovigilance and Patient Safety.

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## Audit of the introduction of MyMathlab for first year and second year MPharm students

**Majdi Garsan Algarsan**
University of Hertfordshire, UK

Numeracy skills are needed by both adults and children in their daily activities. Improving numeracy skills in whatever possible method is important for better performance in every work of life. Doctors, Nurses and Pharmacists need to be very skillful in numeracy in determining doses or administering medicines. Pharmacy students during training must improve their numeracy. Numeracy skills are important for the daily practice of pharmacists to be able to determine doses of drugs. There were incidents where due to error in calculation during the formulation of a medicine that cause the death of some pediatric patients. The peppermint incident is an example of the important requirement of numeracy skills. Medication errors cost the NHS about 750 million pounds annually and dosage errors from calculations are part of them which are mainly due to errors in calculations. The aim of the study was to find out the numeracy skills of MPharm year 1 and year 2 students at University of Hertfordshire and to find out effect of MyMathLab in improving numeracy skills of this group of students. MPharm student in year 1 and 2 were selected from the University of Hertfordshire. Research was done in two segments. Exams and questionnaire send to students by email. Students were given three sets of exam: Induction, Formative and Summative. Exams were marked and analyzed statistically using One-way ANOVA. The questionnaire was made using a programme called 'Survey Monkey'. The questionnaire explored their demographics and what they thought of the numeracy support on their course. Statistical analysis such as the CHI-Square test was applied to the results from the online questionnaire to find out if the results were significant. Themed analysis was completed on the transcribed data for student`s feedback from the Questionnaire.

### Biography

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## The distribution of CYP2B6 variants in Roma from Croatia

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The ADME genes exhibit significant variation among the human populations due to the past demographic and evolutionary events. Genetic distinctiveness is especially pronounced in isolated populations where the exchange of genes with other populations is minimal and where the increased frequency of otherwise rare or private alleles emerges. The example of such population are the Roma, the transnational minority population of Indian origin with centuries long sociocultural isolation which left traces in their gene pool showing considerable differences in comparison to other populations. Therefore, we investigated the variation of a large panel of ADME genes among several Roma minority populations residing in Croatia. Here we present the results of CYP2B6 gene variation which was detected by genotyping five SNP loci (rs12721655, rs2279343, rs28399499, rs34097093, rs3745274, rs7260329, rs8192709) in the three socioculturally and geographically distinct Roma populations living in northern, central and eastern regions of Croatia. Two of the investigated loci (rs28399499, rs34097093) were monomorphic in all samples, while locus rs12721655 was polymorphic only in Roma population from the northern Croatian region of Medjimurje. Its MAF was 21.5% that is considerably high since the global MAF is <1%. MAFs of other loci (rs2279343, rs3745274, rs7260329, rs8192709) ranged from 17-30%, 12-26%, 24-45%, 5-17%, respectively, which is mostly in concordance with their global distributions. The exact test of population differentiation based on genotype frequencies showed marked differences between populations. Significant LD values between pairs of loci were detected in all tree investigated populations. The results indicate the Roma population's distinctiveness and provide a theoretical basis for safer drug administration that may be relevant for treating diseases in this population.

### Biography

In the year 1985. Branka Janicijevic has completed her Ph.D. in Biology ,Faculty of Natural Sciences and Mathematics, University of Zagreb, Croatia. She is a Research Professor of Anthropology at the Institute for Anthropological Research in Zagreb and Professor of Anthropology, Faculty of Humanities and Social Sciences, University of Zagreb, Croatia. Her research interests are interdisciplinary biocultural research of isolated populations, population genetics and molecular anthropology. According to Web of Knowledge database she had 89 scientific papers, 1813 citations and h-index is 20.

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## Epidemiologic study based on Adverse Drug Events in patients visiting Emergency Department: A retrospective Observational Study in Three University Hospital

**Min-Gyu Kang[1], Ju-Yeun Lee[3], Tae-Ho Lim[4], Byoung Whui Choi[2], Chan-Woong Kim[5], Baegeum Kim[3], Ho Joo Yoon[6], Sang-Heon Kim[6],** and **Jae-Woo Jung[2]**

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**Background**: Adverse drug events (ADE) has been recognized as an important cause of serious morbidity and mortality. Severe cases of ADE requires immediate medical treatment including Emergency Department (ED) visits. However, the epidemiologic features of ADE leading to ED visits have not been well described in Korea. We aimed to estimate the prevalence and features of ADE leading to ED visits.

**Methods**: In this retrospective observational study, we reviewed all the cases of ED visits for six months, from July 2014 to December 2014, in two university hospitals in Seoul and a university hospital in Cheongju in South Korea. By reviewing all the medical records including National Emergency Department Information System Database, we identified cases of ADE and assessed the causative drugs, severity, types and preventability.

**Results**: The most common causative drugs of ADE was antineoplastic drugs, insulin and antidiabetic drugs, antithrombic or antiplatelet agents and vaccines. In terms of system of clinical manifestations, gastrointestinal, skin, body as a whole, neurologic and metabolic/nutritional symptoms were most frequent. The most common diagnoses of ADE were complication of insulin (and antidiabetic drugs), complication of antithrombic (or antiplatelet) agents, dizziness, generalized skin rash, gastritis, and neutropenia

**Conclusion**: The prevalence of ADE in ED visits was common Korea and higher in older adults and females. Many cases of ADEs were preventable and predictable. Further prospective study is needed to evaluate the nationwide burden of ADE leading to ED visits.

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## Bronchoprovocation study of Albuterol inhalation on asthma patients: A Pharmacodynamic Bioequivalence Study

**Nailesh Patel** and **Rashmin Patel**
Department of Pharmacology, S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana, Gujarat, India.

**Objective**: The main objective of the study is to determine the clinical endpoints bioequivalence between Test and Reference Albuterol inhalation formulation & to find out the superiority of test over placebo.

**Methods**: The study was conducted in asthma patients of either gender with methacholine challenge. Patients with known surgical histories, known and suspected cases of allergies and pregnant woman's were excluded from this study. Total 260 patients were included. The design of the study was single-dose, double-blind, double dummy, randomized, crossover study with washout of at least 24 hours.

**Result**: Post-dose PC20 or PD20, which are the provocative concentration or dose, respectively, of the methacholine challenge agent required to reduce the forced expiratory volume in one second (FEV1) by 20% following administration of differing doses of albuterol (or placebo) by inhalation is 15.84±0.02. The 20% reduction in FEV1 is determined relative to the saline FEV1 measured before the placebo or albuterol administration. A significant dose-effect relationship was present ($p < 0.0001$). Deviation from parallelism of the test and reference dose-response curves ($p = 0.95$) and differences in overall mean response between the two formulations ($p = 0.68$) were not significant. The calculated 90% CI was 78.86-144.87% for FEV1. There were no serious adverse events observed during the study.

**Conclusion**: The 90% CI for the relative bioavailability (F) falls within the defined bioequivalence limit, i.e., 67.00-150.00%. Hence, it is concluded that Albuterol test formulation is bioequivalent to reference Albuterol formulation.

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## Accepted Abstracts




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## CYP3A time-dependent inhibition risk assessment using inactivation rate

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Time dependent inhibition (TDI) has become the focus of drug designers much more than reversible inhibition because of the higher safety risk this mode of inhibition carries with it. The IC50 shift is the most commonly used method to risk assess TDI because it can be easily tested with modification of the standard, readily automated, reversible CYP3A inhibition testing procedures. This particular inhibition mechanism was indeed the source of a few documented late stage failures and is strongly suspected to participate in the frequently disqualifying liver toxicities in pre-clinical species. We measured kinetic inactivation parameters $K_I$ and $k_{inact}$ for 63 known CYP3A inactivators using a single robust method and validated a miniaturised screening assay based on inactivation rate ($k_{obs}$) at 10 µM test article concentration versus the current gold standard assay. The inactivation rate constant of a large set of registered drugs (400) has been used to highlight the specific advantages of this method versus the $IC_{50}$ shift. Using an empirically defined positive/negative $k_{obs}$ bin of 0.02 min-1, 4% of registered drugs only were found positive. This proportion increased to more than 20% when in-house lead optimization molecules were considered, emphasizing the importance of filtering this property out when selecting promising drug candidates. Finally, we suggest that the data and technology described here may be a good basis for building structure activity relationships and *in silico* modelling.

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## Management of cross-reactivity among sulfonamides: A case report

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A patient developed agranulocytosis after introduction of sulfonylurea agent. According to the Regional Pharmacovigilance Center (CRPV) it was a true hypersensitivity reaction. A month later, the patient is hospitalized for a bronchial infection where multidrug-resistant bacterium is highlighted. The antibiogram shows the interest of sulfamethoxazole and the physician asked pharmacists for the management strategy. Sulfonamides are classified into 3 distinct groups based on their chemical structure: the sulfonylarylamines (including sulfonamide antibiotics), non sulfonylarylamines (including the sulfonylureas) and the sulfonamide derivatives. Analysis of the literature indicated that cross-reaction among different classes of sulfonamide drugs is unlikely to occur, especially between antibacterial sulfonamide and non-sulfa antibiotics because of their difference in structure. An immunoallergic response usually occurs within the first 48 hours in the re-entry of the causal treatment or in case of cross-reaction with a drug of similar chemical structure. In the absence of potential therapeutic alternative, the sulfamethoxazole was introduced with a close biological monitoring. The clinical and biological evolution has been favorable. Among the antibiotics, sulfa allergy is the most common allergy after the beta-lactams. 3% of patients treated with sulfonamides antibiotics develop a severe allergy. In contrast the risk is very rare with non-antibiotic sulfonamides. This case illustrates the collaboration between physicians, pharmacists and the CRPV in the management of complex therapeutic issues. The risk of cross-reactivity between different sulfonamides exists but it is very rare and reintroduction is discussed depending on the severity of the adverse event occurred previously and the risks and benefits of the therapy.

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## Characteristics of sildenafil citrate users in Addis Ababa, Ethiopia

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**Background**: Misuse of sildenafil citrate by healthy young men for recreational purpose is becoming a major concern. The main sources for this are medicine retail outlets (i.e. pharmacies and drug stores).The aims of this study were to describe the characteristics of sildenafil citrate users and to assess the dispensing practice of sildenafil citrate, in community pharmacies in Addis Ababa, Ethiopia.

**Methods**: A survey was conducted among customers who purchased sildenafil citrate from community pharmacies in May 2013; and semi-structured interviews were conducted with community pharmacists. Quantitative data was analyzed by using simple descriptive statistics. For the interviews, thematic analysis was used.

**Results**: More than half of the respondents to the survey (n=197) were below 40 years (57.9%), never married (53.8%) and had post high school study (57.9%). All were men. Only 16.6% of them were diagnosed for ED, and 58.4% had used sildenafil before. The main reason for buying sildenafil was experimentation (46.9%). According to interviewees sildenafil citrate was found being dispensed without prescription due to unhealthy competition among medicine retail outlets and clinics. Dispensing the medicine without adequate counseling and provision of information was also reported.

**Conclusion**: Respondents of all age groups were found using sildenafil citrate mainly without confirming the appropriateness of the etiologic conditions. Selling sildenafil without a prescription seems to be a common practice in pharmacies in Addis Ababa. Strengthening the regulatory activity is crucial to ensure that customers are protected from unprecedented health risk in the dispensing of medicines.

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## Epidemiology and economic burden of adverse drug reactions & their risk factors among Indian ambulatory patients- role of clinical pharmacist

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Now a days ,ADRs are the important cause of hospital admissions, constituting a significant economic burden.We thus aimed at identifying ADRs and assessing their causality, preventability and severity,risk factors & economic burden in Indian ambulatory patients over a 6 months period. Of the total 400 prescriptions, 138 (34.5%) were identified with ADRs. Using the Naranjo's algorithm, it was found that ,48 ADR's were definite, 57 were probable & 33 were possible .Severity was assessed using Modified Hartwig and Siegel scale,in which 45 (32.6%) patients had mild ADRs,66 (47.8%) had ADRs of moderate severity and 27 (19.56%) had severe ADRs. Schumock and Thornton scale was used to identify the preventability of ADR's among which 36 (26.08%) ADR's were definitely preventable, 74 (53.62%) were probably preventable & 28 (20.28%) were not preventable .mean hospital stay of patients was 8 days & average cost per patient suffered with an ADR was INR 3,751/-. Risk increases with age (> 60) , gender (females) , number of prescribers (>2), prescription of multiple drugs (>5) , duration of treatment (>1 month), multiple diagnoses. Most commonly observed ADR'S were anti-tubercular drugs induced hepatotoxicity,calcium channel blockers induced edema , ACE inhibitors induced dry cough, olanzapine caused diabetes mellitus. The awareness of risk factors of ADRs would help physicians to identify patients with greater risk & therefore, might benefit from ADRs monitoring and reporting programme. Thus clinical pharmacist has a role in conducting medication history interview and dose tailoring there by influencing the prevention of economic burden to the patients.

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# 6th Pharmacovigilance Congress



## Evaluation of a pediatric liquid formulation to improve 6-mercaptopurine therapy in children

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6-mercaptopurine has until recently had no adequate formulation for pediatric patients with acute lymphoblastic leukemia (ALL). The only oral paraben-free 6-MP liquid formulation named Loulla was developed and evaluated in the target population. Preclinical and clinical evaluation was performed according to a Pediatric Investigation Plan, in order to apply for a Pediatric Use Marketing Authorization. The pre-clinical study assessed the maximum tolerated dosage-volume and evaluated local mucosal toxicity of 28 daily administrations in treated compared to controls gold hamsters. The multi-centre clinical study was single-dose, open-label, crossover trial, conducted in 15 ALL children during maintenance therapy. Bioavailability and palatability of a single 50 mg fixed dose of Loulla compared to 50 mg registered tablets were evaluated in a random order on two consecutive days. Seven blood samples over 9 hours were obtained each day at to determine pharmacokinetic parameters, including Tmax, Cmax, $AUC_{0-9}$ and $AU_{C0-\infty}$. A questionnaire adapted to children testing Loulla palatability and preference for either Loulla or the usual 6-MP tablet was completed. Occurrence of adverse events was determined at study visits by vital sign measurements, patient's spontaneous reporting, investigator's questioning and clinical examination. The dosage-volume of 75 mg/kg/day was well tolerated in gold hamster. The relative bioavailability of liquid Loulla formulation compared to the reference presentation is 76% for AUCs and 80% for Cmax. The taste of Loulla and the mouth feeling after ingestion compare favorably to the tablet. No adverse event occurred. Pharmacokinetic, palatability and safety data support the use of Loulla in children.

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## Increase and effectiveness in the activity of audits of quality in the Center of Genetic Engineering and Biotechnology

**Mariela Díaz Cinza**
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This poster presentation aims at sharing the experiences of a study carried out by a group of researchers who audited the quality at the Center of Genetic Engineering and Biotechnology in Havana, Cuba, by means of its correct planning and control. For this purpose, bibliographical review as well as methods such as interviews, brainstorming, group decision-making and causes-effect diagrams was necessary. The application of the methods made it possible to carry out the diagnosis and analysis of the situation and to give a solution to the problem. The diagnosis showed that the activity does not guarantee a continuous improvement of the processes and quality of the system. Some actions were implemented, such as: Upgrading the procedures and forms of the activity, creating an organizational structure and making audit programs to accomplish different activities and processes. These actions rendered remarkable results for audits, since they included the evaluation by suppliers, the internal audits and the protocols, final reports and critical phases of the preclinical and clinical tests.

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## That's how you make drugs!

**H C Peter Kapitein**
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The path a drug has to travel from its early beginnings until it reaches the patient is a long one. The entire process is divided into dozens of stages, possibly even hundreds. No one monitors or takes responsibility for the entire process. However, the patients are the ones who pay the price. Patients do not really have a say in any of the groups that are involved in bringing a drug to the market. David Tuveson, a leading pancreatic cancer researcher asked me what the most important thing was that pancreatic cancer patients had to deal with? My answer was: 'Pain!' David's conclusion; 'If I can take away the pain I give them six to twelve months more Peter'. However, nobody apart from David does any research into the pain related to pancreatic cancer. Relevant research and the relevant drugs and clinical trials that result from them arise through cooperation between patients, physicians, scientists and representatives of the pharmaceutical industry. Patients will also indicate that the introduction of new medicines takes far too long and can be much quicker. In conclusion, patients do not need treatments that don't work or which have horrific side-effects. This is however the effect of most treatments so far. To date this has involved spending considerable amounts of money, which in most cases has just led to misery. Listening to and cooperating with patients is not only beneficial for them, but also for the healthcare services and the related costs.

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## Hypothalamic cytokine as biomembrane stabilizer

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**Aim**: The aim of the given work was to investigate the membranous aspects of the development of endogenous intoxication under radiation stress and the possibilities of its correction by studying the changes of the main lipid and protein components of biomembranes before and after introduction of proline-rich polipeptide-hypothalamic cytokine (HC).

**Materials & Methods**: The test subjects were Wistar white male rats. The animals were exposed to ionizing irradiation. After 10 days of the exposure 3 Grey of HC was introduced intraperitoneally for 3 days at a rate of 5 mg per 100 g of animal's weight.

**Results**: It is determined that the radiation stress is characterized by considerable metabolic derangements of the main classes of membranous phospholipids (PL) lymphocytes, thymocytes, and the cells of spleen tissue. Moreover, a double reduction of the activity of cytoplasmic glycerophosphate dehydrogenase and glycerol kinase is observed. At the same time a simultaneous, more than triple, increase of the activity of phospholipase A2 and of the processes of peroxide oxidation of lipids (POL) is observed. On the background of considerable ($P<0.01$) increase of the levels of lysophospholipids, phosphatidic acids and adenosine monophosphate, a reduction of the content of phosphatidylcholines and phosphatidylserines, as well as an inhibition of potency of Na/K- and Mg-ATP in spleen tissue and in blood lymphocytes is observed. After application of HC, a definite normalization of membranous phosphatidylserines and the activity of enzymes of phosphatidogenesis are observed. On the background of restoration of the content of adenosine monophosphates and ATP, the activity of ATP system, potency of phospholipase A2 and processes of POL is almost totally normalized. Possible mechanisms of development of endogenous intoxication under the radiation stress and its correction under the action of HC are being discussed.

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## Evaluation of drugs removed from the United States market from 2000 to 2015

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This study was conducted to collect and analyze data on prescription drugs removed from the United States market from 2000 to 2015. Information was initially obtained from the FDA website and then augmented with data from primary literature. Medline was the primary bibliographic database utilized with withdrawn drug names as keywords. Inquiry was also done on drugs that were later reinstated and drugs that only had a single dosage form removed from the market. A total of 26 drugs were withdrawn from the market during the time period researched. Three drugs were withdrawn then reinstated and 5 drugs had a certain dosage form withdrawn. The top 3 drug classes removed were: Biological response modifiers (19.2%), gastrointestinal agents (15.3%) and psychotropic agents (15.3%). The top three reasons drugs were withdrawn from the market were cardiotoxicity, hepatotoxicity and stroke. Of the agents withdrawn, the average time on the market was 9.0 years +/- 6.2. The median and mode were 8.5 and 4.0 years respectively. These were calculated removing the outliers which are propoxyphene (52.0 years) and pemoline (30.3 years). It appears that the top classes of drugs withdrawn from the market and the reasons for removal have changed in the past 13 years as compared to earlier findings by others. Reported prolonged periods of drugs in the market before removal may necessitate a strict monitoring of both efficacy and toxicity once drugs are approved.

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## Pharmacovigilance education for medical students

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In 2006, the Institute of Medicine reported in Preventing Medication Errors that at least 1.5 million preventable adverse drug events occur each year in the USA. A related concern may be whether there is an increase in poor patient outcomes in July, when newly trained medical residents enter practice. Although most such reports are anecdotal, such as "Don't get sick in July", there are also peer-reviewed studies. For example, the highest risk myocardial infarction patients suffer increased mortality in July in hospitals that are categorized as teaching intensive. Most pharmacology education in USA medical schools occurs in the early years of the medical school curriculum through some introduction to basic principles of pharmacodynamics and pharmacokinetics and then system-specific drug coverage that is often integrated into system-based pathophysiology units. Clinical pharmacology coverage in later years of the curriculum is rarely required but more often offered as an elective. To provide consistent and universal education on the topics of adverse drug events and pharmacovigilance, we instituted a four-part module in the year-2 medical student curriculum. We first provide a concise self-study packet of principles and then have faculty facilitation for 3 case-based, small group discussion sessions, with the adverse event cases specifically designed to integrate material across systems. We assess knowledge through multiple-choice questions in the regular course examinations. Student evaluation of these sessions has been very positive. The pharmacovigilance curriculum has become a key component of our longitudinal curricular theme on patient safety and quality improvement.

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## Cytoprotective effect of *Hypericum triquetrifolium turra*. On cyclophosphamide–induced cardiotoxicity in rat

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Cardiotoxicity is one of the limiting side effects of this commonly used anticancer agent and cardiotoxic effects of CP were found to be dose-related cardiac damage, morphologically defined necrosis, bleeding. *Hypericum triquetrifolium Turra.*(HT) is a phenolic component with antioxidative and anticarciogenic properties. This study aimed to investigate the possible protective effect of HT on CP-induced cardiotoxicity. Serum aspartat transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), malondialdehyde (MDA), creatine kinase-MB (CK-MB), total oxidant state (TOS), total antioxidant state (TAS), oxidative stress index (OSI) was examined. Furthermore, the cardiac tissues were analysed histologically. Albino rats (Wistar, 3-4 months old, male, weight 220 ± 20 g healthy) were randomly divided in 9 groups, each including seven animals: Group 1 (control) treated with 0,5ml saline; groups 2 treated with 150 mg/kg CP, respectively; group 3, 4 and 5 treated with 25, 50 and 100 mg/kg HT; groups 6 , 7 and 8 treated with 25, 50 or 100 mg/kg HT+CP, group 9 treated with 0,5ml - %0,2 DMSO. The results was analyzed bye One Way Analysis of Variance and Kruskal-Wallis One Way Analysis of Variance on Ranks Test. Levels of AST, ALT, LDH, MDA, CK-MB, TOS, OSI were found high only in the CP groups. GSH and TAS levels were found low in the only CP groups. There was a dose-dependent on the CP-induced cardiotoxicity. Hemorrhage, inflammatory cell infiltration and the separation of the muscle fibers in the heart tissue supported the biochemical data. With 25, 50, 100 mg/kg HT, there was an important decrease in the CP toxicity and reduced inflammation and lipid peroxidation in the heart tissue and increase of serum glutathione (GSH) and total antioxidant capacity (TAS) levels were found when HT was applied. Based on these findings, it could be proposed that HT was a strong candidate in preventing the CP-induced cardiotoxicity but further clinical studies should be done in order to verify its application on humans.

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## Healthcare providers' knowledge and their counseling practice about warfarin in the university teaching tertiary care hospital, addis ababa, ethiopia

**Tamrat Assefa**
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**Objective**: The main objective was to assess healthcare providers' knowledge about warfarin and their counseling practice on warfarin at Tikur Anbessa Specialized Hospital (TASH).

**Material and Methods**: Cross sectional study design which included 164 pharmacists and physicians was conducted at TASH, Addis Ababa Ethiopia. The assessment was through questionnaire which consisted of 15 multiple choice questions on warfarin knowledge and 4 questions on counseling practice about warfarin (multiple choice and open ended questions).The data was analyzed with SPSS and the differences between groups were compared using one-way ANOVA followed by turkey's post-hoc test.

**Results**: Out of 15 questions the mean total score was 9.98 (SD=1.67).Among study participants, there was no one who gave correct answers to all questions. The total score of the overall test were (9.45 + 1.63) by pharmacists, (10.06 + 1.49) by interns and (10.35 + 1.77) by residents. In their counseling practice, among the total study participants, 61.6% and 29.3% of them responded as they provide counseling services for all and only for new patients who are on warfarin respectively. Among the factors which have influence on their counseling practice insufficient time and poor counseling environment predominantly affect 54.3% and 32.9% of study participants respectively.

**Conclusion**: Based on this study finding it can be concluded that the knowledge of healthcare providers regarding oral anticoagulation was inadequate. Residents had better knowledge than pharmacists and interns on questions related to warfarin. The study participants had different experience on providing counseling for patients on warfarin.

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## Evaluation of medication adherence among Lebanese diabetic patients

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**Introduction**: Diabetes type II (DTII) is one of the major public health concerns. Despite the progress made in the treatment of DTII over the years, lack of adherence to diabetic treatment is associated with sub-optimal treatment efficacy and poor glycemic control. The main objective of this study is to evaluate the adherence of DTII Lebanese patients to non-insulin antidiabetic treatment. The secondary objective was to determine the factors influencing this adherence.

**Methods**: A cross-sectional study was conducted on a sample of Lebanese diabetic patients selected from private clinics and clinics located in several hospitals in Beirut, Lebanon. Data was collected using a questionnaire filled by trained interviewers, and the level of adherence was measured using the scale of Morisky (8-item Morisky Medication Adherence Scale: 8-MMAS). Bivariate and multivariate analyses were conducted using SPSS version 20.

**Results**: The majority of the population were women (54.3%) and obese (47.8%). Only 20.4% followed a diet recommended by the physician and 29% attained the glycemic control target of HbA1C less than 7%. Among the 245 patients who were included, 31.8% had high adherence, 31.1% had medium adherence, and 37.1% had low adherence. Mean 8-MMAS score was 5.81±2.27. According to the bivariate analysis, following physical activity ($p=0.001$), diet recommended by physician ($p<0.001$), glycemic control ($p=0.031$), and visits to the endocrinologist ($p<0.001$) were positively associated with medication adherence; while taking sulfonylureas ($p=0.026$), presence of chronic obstructive pulmonary disease/asthma ($p=0.037$), occurrence of adverse events ($p=0.024$), presence of complications ($p=0.004$), and polymedication ($p=0.016$) are the most important factors associated negatively with the drug adherence. The fact that the treatment showed a heavy burden ($p<0.001$), drug discontinuation according to the state of health ($p<0.001$), traveling ($p<0.001$), glycemic disorder ($p=0.009$), forgetfulness ($p<0.001$), high cost of drugs ($p=0.007$), complexity of treatment ($p=0.001$), and its ineffectiveness ($p=0.003$) were predictors of poor adherence in a multiple linear regression. Logistic regression showed that the increase of working hours ($p=0.01$), following the advice given by the relatives not by physician ($p=0.048$), and skipping or doubling the dose ($p=0.001$) were associated with a decrease in the level of adherence. Furthermore, females ($p=0.037$), and elderly ($p=0.015$) were more likely to have low medication adherence, while following of diet ($p=0.012$), and instructions ($p<0.001$) recommended by physician contributed to medication adherence as a protective factor.

**Conclusion**: Medication adherence is sub-optimal in Lebanon and the glycemic control remains difficult to establish. The development of intervention programs and education strategies are needed to solve these identified factors. A more intensive communication between patients and health professionals is an essential step in improving medication adherence in order to prevent the complications and reduce death rate.

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## Update on cardiotoxicity and safety of Domperidone for treating nausea and vomiting

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**Background**: Domperidone, a dopamine receptor antagonist, acts peripherally as a gastrointestinal prokinetic and centrally as an anti-emetic. A safety concern in regards to domperidone is whether it can cause ventricular arrhythmia and sudden cardiac death.

**Objectives**: This systematic review has been designed to address whether there is any possible association between domperidone and serious cardiac events such as ventricular arrhythmia or sudden cardiac death.

**Data sources, study eligibility criteria & participants**: PubMed was searched for case-control studies on the cardiotoxicity associated with domperidone. Moreover, clinical studies on the effects of domperidone in patients with gastroparesis were reviewed for any cardiac adverse events.

**Study appraisal and synthesis methods**: Seven case-control studies and 7 interventional studies were retrieved. The quality of case-control studies were tested by the Newcastle-Ottawa Scale (NOS) based on its 3 major criteria, i.e. selection, comparability and exposure, where good quality research is defined as ≥ 3 points for the selection domain, ≥ 2 points for the comparability domain and ≥ 2 points for the exposure domain. The odds of domperidone on outcome were assessed. Random and fixed effect models were used based on I2 value. The rate of cardiac events in interventional studies was also determined.

**Findings**: Most of the included case-control studies were graded fair or poor based on NOS, although mathematically domperidone was a significant risk for cardiac events (unadjusted Odds ratio: 1.88 and adjusted Odds ratio 1.60; $P<0.05$). Serious cardiac adverse effects were not reported in the patients with gastroparesis using domperidone at the dosage range of 30-120mg (majority ≥80 mg) daily for up to 48 months. In the most recent study, 64 patients were receiving domperidone (40 to 120 mg daily) for various time intervals from 3 months to 4 years; 52 for gastroparesis and 8 for chronic nausea and vomiting. Approximately 73% of the patients had a clinically meaningful response to domperidone and there were no serious side effect. Only 3 of the 64 patients chronically receiving high doses of domperidone reported palpitations but without any complaints of chest pain or accompanying QTc prolongation or cardiac dysrhythmias.

**Limitations**: As mentioned, the quality of most of the included case-control studies was of fair or poor grading. Some of the included studies in meta-analysis had low prevalence of patients exposed to domperidone. This may provide biased effect size. Conclusions and implications of key findings: Due to the low quality of case-control studies on the cardiotoxicity of domperidone, the possible association between this medication and cardiac events is still under debate. Although, this association is not adequately clear, we should be cautious when prescribing this medication. Well-planned prospective studies should explore the long-term adverse effects of domperidone.

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