

РЕЗЮМЕТА НА НАУЧНИТЕ ПУБЛИКАЦИИ

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за участие в конкурс за заемане на академичната длъжност „*професор*” по „Фармакология (вкл. фармакокинетика и химиотерапия)“, област на висше образование 7. Здравеопазване и спорт, професионално направление 7.1. Медицина

Ganeva M, Gancheva T, Troeva J, Kiriyaq N, Hristakieva E. Clinical relevance of drug-drug interactions in hospitalized dermatology patients. *Advances in Clinical and Experimental Medicine*, 2013;22 (4):555-563.

IF=0,333**Abstract**

Background. Potential drug-drug interactions (DDIs) are known to be a risk factor for the development of adverse drug reactions (ADRs). Data on the occurrence of ADRs related to DDIs is scarce and comes from different groups of patients.

Objectives. The aim of the study was to evaluate the frequency, nature and determinants of potential DDIs in hospitalized dermatology patients and assess their contribution for the development of ADRs.

Material and Methods. A prospective observational study comprising all consecutive inpatients admitted to the Clinic of Dermatology and Venereology, University Hospital, Stara Zagora for the period March 2009 – August 2011 was carried out. Systemic medication was screened for potential DDIs using an electronic drug interactions checker. DDIs were then verified with Stockley’s Drug Interactions and divided into “clinically important” and “clinically unimportant”. ADRs were classified by clinical manifestation, type and severity. Causality was scored according to Naranjo et al. (1981).

Results. The study included 674 patients, 513 (76.1%) of them with established comorbidities. Totally, 504 potential DDIs were identified (441 “clinically important” and 63 “clinically unimportant”) in 236 patients. Hypotension was the most common expected clinical presentation of the potential DDIs. The strongest predictor for the development of DDIs was the number of systemic drugs (OR 2.25, 95% CI 1.97–2.58). Overall 43 ADRs were recorded, 53.5% “type B” and 46.5% “type A” reactions, most commonly with cutaneous and cardiovascular manifestations. The development of ADRs was attributed to 13 DDIs (2.6% of all detected potential DDIs) in 10 of these cases (23.25%).

Conclusions. Potential DDIs were frequent in hospitalized dermatology patients. The drug groups most commonly involved were cardiovascular drugs. The proportion of DDIs associated with the occurrence of ADRs was relatively low, but close monitoring of patients on multiple drug regimens is essential because these reactions may be severe.

Keywords: drug-drug interaction, adverse drug reaction, hospital, dermatology.

Ivanova M, Manolova I, **Ganeva M**, Gancheva R, Stoilov R, Stanilova S. Elevated serum levels of TH17-related cytokines in patients with ankylosing spondylitis. *Journal of the Balkan Tribological Association*, 2016, 22(3-II):2638-2651, **IF=0,737**

Abstract

Dysregulation of cytokine production or action is thought to have a central role in the development of autoimmunity and autoimmune disease. The aim of this study was to analyze serum TNF- α , IL-18, IL-12p40, IL-17 and IL-23 in patients with ankylosing spondylitis (AS) and their relation to disease activity and treatment regimens. Cytokines in the serum of 77 AS patients and 48 age- and sex-matched healthy controls were measured by ELISA assay. Disease activity was assessed by the ASDAS-CRP, ESR and CRP. Serum levels of most of the studied pro-inflammatory cytokines were elevated in AS patients compared to healthy subjects; IL23, IL-17 and IL-18 were significantly higher ($p<0.001$), whereas TNF- α was higher but not significantly elevated. The cytokine concentrations between subgroups upon TNF - specific blockade

and non-anti-TNF therapy were comparable and not statistically different for all cytokines, but, notably, TNF- α was numerically higher in patients upon treatment with anti-TNF. No association was calculated between TNF- α , IL-17 и IL-23 with the ASDAS-CRP and both inflammatory biomarkers. Only a weak correlation between IL-18 and ASDAS-CRP and between IL-12p40 and CRP was found, because of which we consider that the investigated cytokines are poor indicators of activity in this disease and do not reflect it accurately.

Keywords: TNF- α , IL-18, IL-12p40, IL-17, IL-23, ankylosing spondylitis, disease activity, therapy.

Brinkman DJ, Tichelaar J, Mookink LB, Christiaens T, Likic R, Maciulaitis R, Costa J, Sanz EJ, Maxwell SR, Richir MC, van Agtmael MA... R Lefebvre, I Kostadinova, **M Ganeva**...for the Education Working Group of the European Association for Clinical Pharmacology and Therapeutics (EACPT) and its affiliated Network of Teachers in Pharmacotherapy (NOTIP). Key Learning Outcomes for Clinical Pharmacology and Therapeutics Education in Europe: A Modified Delphi Study. *Clinical Pharmacology and Therapeutics*, 2018, 104(2): 317-325 **IF=6,336**

Abstract

Harmonizing clinical pharmacology and therapeutics (CPT) education in Europe is necessary to ensure that the prescribing competency of future doctors is of a uniform high standard. As there are currently no uniform requirements, our aim was to achieve consensus on key learning outcomes for undergraduate CPT education in Europe. We used a modified Delphi method consisting of three questionnaire rounds and a panel meeting. A total of 129 experts from 27 European countries were asked to rate 307 learning outcomes. In all, 92 experts (71%) completed all three questionnaire rounds, and 33 experts (26%) attended the meeting. 232 learning outcomes from the original list, 15 newly suggested and 5 rephrased outcomes were included. These 252 learning outcomes should be included in undergraduate CPT curricula to ensure that European graduates are able to prescribe safely and effectively. We provide a blueprint of a European core curriculum describing when and how the learning outcomes might be acquired.

Pashova-Stoyanova L, Tolekova A, **Ganeva M**, Tsokeva Zh, Hadzhibozheva P, Georgiev Ts, Nancheva Kr. Vitamin D effects on lipid profile and uric acid levels in the experimental model of metabolic disorders in fructose fed wistar rats. *Farmacia*, 2019, 67(6):1071-1076 **IF=1.607**

Abstract

A growing number of studies suggest that hyperuricemia and low vitamin D levels could contribute to the pathogenesis of metabolic disorders and the development of metabolic syndrome and vice versa - the development of metabolic disorders itself could lead to low vitamin D levels and high uric acid levels. The present study aims to investigate the role of vitamin D effects on uric acid levels and lipid profile in the experimental model of metabolic disorders in fructose fed male Wistar rats. In our study we confirmed the protective role of vitamin D and its effects in lowering the elevated uric acid levels. Vitamin D decreases glucose and uric acid concentrations and improves the cardiogenic lipid profile (cholesterol/HDL and LDL/HDL).

Keywords: vitamin D, uric acid, metabolic disorders

Tsokeva Zh, **Ganeva M**, Gancheva T, Hristakieva E. Dietary supplements – use and safety perception: A study among hospitalized dermatology patients. *International Journal of Clinical Pharmacology and Therapeutics*, 2021, 59(2):116-126. DOI10.5414/CP203857 2021 **IF=0.976**

Abstract

Objectives: Evidence suggests that the use of dietary supplements in patients with various disorders is growing. The study aims to examine the use of drug supplements in patients with dermatological disorders, regarding their type, the reasons and predictors of their use, and the safety beliefs and communication attitude of users. **Materials and methods:** A cross-sectional study of patients hospitalized in the Clinic of

Dermatology and Venereology at the University Hospital in Stara Zagora, Bulgaria, was carried out from October 2018 to December 2019. Data were collected using a specially designed and validated questionnaire. Statistical analysis included the χ^2 -test, the Mann-Whitney U test, and logistic regression.

Results: Overall 348 patients (204 females and 144 males) were involved in the study. The patients who reported having used dietary supplements were 67% of the study population. Various combinations ranked first among the dietary supplement types, and vitamins/minerals presented a substantial part (75.9%). The majority of the patients (61.6%) used dietary supplements for more than one reason, mainly for organ-related disorders. Most of the respondents (76.4%) considered them to be completely safe. Higher education (OR = 1.91; CI: 1.14 – 3.19), being a non-smoker (OR = 1.81; CI: 1.14 – 2.88), and sporting activities (OR = 1.71; CI: 1.03 – 2.83) increased the odds of using dietary supplements. **Conclusion:** The examined cohort of dermatology patients presented a dietary supplement user profile similar to the general population. The study confirmed that these products are considered to be safe by the majority of participants. Factors indicative of a healthy lifestyle and higher education were predictive for their use.

Keywords: dietary supplements, use, safety beliefs, dermatology

Bakkum MJ, Tichelaar J, Papaioannidou P, Likic R, Sanz EJ, Christiaens T, Costa JN, Mačiulaitis R, Dima L, Coleman J, Richir MC, van Agtmael MA, Atanasova I, **Ganeva M**, Gatchev E... Harmonizing and improving European education in prescribing: An overview of digital educational resources used in clinical pharmacology and therapeutics. *British Journal of Clinical Pharmacology*, 2021, 87(3):1001-1011 DOI10.1111/bcp.14453

IF=3.716

Abstract

Aim: Improvement and harmonization of European clinical pharmacology and therapeutics (CPT) education is urgently required. Because digital educational resources can be easily shared, adapted to local situations and re-used widely across a variety of educational systems, they may be ideally suited for this purpose.

Methods: With a cross-sectional survey among principal CPT teachers in 279 out of 304 European medical schools, an overview and classification of digital resources was compiled.

Results: Teachers from 95 (34%) medical schools in 26 of 28 EU countries responded, 66 (70%) of whom used digital educational resources in their CPT curriculum. A total of 89 of such resources were described in detail, including e-learning (24%), simulators to teach pharmacokinetics and/or pharmacodynamics (10%), virtual patients (8%), and serious games (5%). Together, these resources covered 235 knowledge-based learning objectives, 88 skills, and 13 attitudes. Only one third (27) of the resources were in-part or totally free and only two were licensed open educational resources (free to use, distribute and adapt). A narrative overview of the largest, free and most novel resources is given.

Conclusion: Digital educational resources, ranging from e-learning to virtual patients and games, are widely used for CPT education in EU medical schools. Learning objectives are based largely on knowledge rather than skills or attitudes. This may be improved by including more real-life clinical case scenarios. Moreover, the majority of resources are neither free nor open. Therefore, with a view to harmonizing international CPT education, more needs to be learned about why CPT teachers are not currently sharing their educational materials.

Keywords: clinical pharmacology and therapeutics, digital, education, open educational resources, prescribing

Bakkum MJ, Richir MC, Papaioannidou P, Likic R, Sanz EJ, Christiaens T, Costa JN, Mačiulaitis R, Dima L, Coleman J, Tichelaar J, van Agtmael MA, Atanasova I, **Ganeva M**, Gatchev E, ... EurOP2E – the European Open Platform for Prescribing Education, a consensus study among clinical pharmacology and therapeutics teachers. *European Journal of Clinical Pharmacology*, 2021, 77(8):1209-1218. **IF=3.064**

Abstract

Purpose Sharing and developing digital educational resources and open educational resources has been proposed as a way to harmonize and improve clinical pharmacology and therapeutics (CPT) education in European medical schools. Previous research, however, has shown that there are barriers to the adoption and implementation of open educational resources. The aim of this study was to determine perceived opportunities and barriers to the use and creation of open educational resources among European CPT teachers and possible solutions for these barriers.

Methods CPT teachers of British and EU medical schools completed an online survey. Opportunities and challenges were identified by thematic analyses and subsequently discussed in an international consensus meeting.

Results Data from 99 CPT teachers from 95 medical schools were analysed. Thirty teachers (30.3%) shared or collaboratively produced digital educational resources. All teachers foresaw opportunities in the more active use of open educational resources, including improving the quality of their teaching. The challenges reported were language barriers, local differences, lack of time, technological issues, difficulties with quality management, and copyright restrictions. Practical solutions for these challenges were discussed and include a peer review system, clear indexing, and use of copyright licenses that permit adaptation of resources.

Keywords: open educational resources, digital education, clinical pharmacology and therapeutics, medical education

Ganeva M, Gancheva T, Deliyska R, Gancheva D, Hristakieva E. Drug-related psoriasis. *Postepy dermatologii i alergologii (Advances in Dermatology and Allergology)* **IF**₂₀₂₁=**1.664** (in press).

Abstract

Psoriasis is a common chronic, systemic immune-mediated, polygenic, and multifactorial skin disorder requiring long-term treatment. The onset of psoriasis or relapses of the disease can be caused by various factors including drugs. The enlarging spectrum of comorbid disease states in psoriasis patients is associated with using a diverse array of medications that may affect the course of psoriatic disease.

We report 2 cases of psoriasis patients with comorbidities: case 1 with PASI score 20,4 and concomitant type 2 diabetes mellitus and arterial hypertension managed with bisoprolol and lisinopril/amlodipine; case 2 with PASI score 32 and idiopathic thrombocytopenic purpura continuously treated with systemic corticosteroids for more than 10 years. No clinical or laboratory indicators of infection were detected. The use of systemic glucocorticosteroids, a beta-blocker, and an ACE inhibitor was considered a psoriasis exacerbating factor.

Evidence suggests that 2 major groups of cardiovascular drugs such as beta-blockers and ACE inhibitors should be used sparingly, if used at all, in psoriasis patients with comorbidities. Although systemic glucocorticosteroids are not included in the present guidelines for the treatment of psoriasis these medications are still largely prescribed in psoriasis patients. For the proper management of polymorbid patients with psoriasis knowledge of the detailed drug history, strict clinical monitoring, and a multidisciplinary approach are necessary.

Keywords: psoriasis, drugs, glucocorticosteroids, beta-blockers, ACE inhibitors

Manolova I, Ivanova M, Stoilov N, Ganeva M. Elevated level of circulating interferon-gamma (IFN- γ) in patients with systemic lupus erythematosus with moderate to severe disease activity and presence of lupus nephritis *Revmatologija (Bulgaria)* 2013, 21(3):54-60 **SJR=0,102**

Abstract

Imbalance between pro-inflammatory and anti-inflammatory cytokines including cytokines produced by T-helper cells is a known characteristic feature of systemic lupus erythematosus (SLE). The aim of the study was to investigate the role of IFN- γ (Th1-cytokine) in the pathogenesis of SLE by measuring its serum concentration in patients with SLE and analyzing the relation between IFN- γ and the clinical manifestation and disease activity of SLE assessed with the SLEDAI index. The study included 54 patients with SLE and 27 healthy subjects. Serum IFN- γ concentration was significantly increased in patients with SLE (mean \pm

SD, 8.48 ± 5.8 ; range, 0.0-36.87) ($p = 0.002$) as compared to controls (mean \pm SD, 4.92 ± 2.9 ; range, 0.0-10.35). Increased level of serum IFN- γ was recorded in patients with moderate and severe activity of the disease, as well as in patients with renal involvement. Serum IFN- γ levels correlated with the SLEDAI index ($R = -0.497$, $p < 0.001$) and decreased levels of C3-complement fraction ($R = -0.34$, $p = 0.019$) in the serum of patients with SLE. These data are consistent with the participation of IFN- γ in the disease activation and the occurrence of lupus nephritis.

Keywords: IFN- γ , systemic lupus erythematosus, lupus nephritis, SLEDAI

Ganeva M, Gancheva T, Troeva J, Gancheva D, Hristakieva E. A study of adverse drug reactions in hospitalized patients in relation to age. *European Journal of Clinical Pharmacy* (former *Atención Farmacéutica*), 2016, 18(3):154 - 162. **SJR=0,111**

Abstract

Background. Older age is generally accepted as a risk factor for Adverse Drug Reactions (ADR). Cutaneous reactions to drugs are a common challenge in everyday medical practice because of their non-specific and variable clinical presentation. The association of age with drug allergy is still less well studied. **Objective.** The aim of the study was to evaluate and compare the characteristics of ADR in different age groups of patients hospitalized for the treatment of dermatological disorders. **Method.** A prospective non-interventional pharmacovigilance study was conducted among patients consecutively hospitalized in the Clinic of Dermatology and Venereology, University Hospital in Stara Zagora, Bulgaria from March 2013 to March 2015. ADR were classified by clinical manifestation, type, causality (according to Naranjo et al., 1981), severity (according to Hartwig et al., 1992) and preventability (according to Hallas et al., 1990). Patients were divided in two age groups: below 65 years and above 65 years. **Results.** For the study period 61 ADR in 58 patients manifesting as skin, metabolic, cardiovascular, vision and other types of disorders were detected. Cutaneous ADR accounted for 60.7% of all ADR. The distribution of ADR according to type yielded 20 (32.8%) «type A» reactions, 34 (55.7%) «type B» reactions, 5 (8.2%) «type C» reactions and 2 (3.3%) «type E» ADR. Regarding causality 37 ADR (60.7%) were scored as «possible» and 24 (39.3%) as «probable». Severity assessment showed that ADR leading to hospital admission classified as «level 4B» reactions (37 or 60.7% of all ADR) were prevalent. Evaluation of ADR preventability revealed that 40 (65.6%) of the reactions were «unavoidable», 15 (24.6%) «possibly avoidable», 5 (8.2%) «definitely avoidable» and 1 (1.6%) «unclassifiable». The study did not identify any significant differences in younger and older patients concerning ADR type, causality and preventability. There was a tendency for some prevalence of «type B» ADR in patients below 65 years of age and significantly more ADR leading to hospitalization ($p=0.03$) in this age group. **Conclusions.** The prevalence of ADR hospital admissions in younger patients in this study is associated with the clinical setting and the detection of more «type B» ADR in dermatology patients. Other patient-related factors like reduced cognitive capacity and communication in the elderly may also play a contributing role.

Keywords: adverse drug reactions – age – elderly – dermatology

Pashova-Stoyanova L, **Ganeva M.** Angiotensin II, angiotensin II receptors and diabetes mellitus. *Current Topics in Pharmacology*, 2016, 20:99-111. **SJR=0,126**

Abstract

Angiotensin II (Ang II), the main effector of the RAS, is closely connected to insulin resistance, diabetes mellitus (DM) and its complications. Ang II carries out its effects mainly through the activation of AT₁ and AT₂ receptor subtypes. The signal transduction mechanisms of the AT₁ receptor typically depend on phospholipase C (PLC), phospholipase D (PLD), phospholipase A₂ (PLA₂) and adenylate cyclase while AT₂ receptor signaling is linked to protein phosphatases and activation of nitric oxide/cGMP system. AT₁ receptor activation is associated with vasoconstriction growth, inflammation whereas AT₂ receptor activation leads to vasodilation, anti-inflammatory and, antiapoptotic action. RAS contributes to insulin resistance and endothelial dysfunction in DM through the modulation of insulin signaling. It is hypothesized

that in DM AT₂ receptors are downregulated thus leaving AT₁ receptors unopposed. The disbalance between AT₁- and AT₂ receptor-mediated signaling and the rise in Ang II levels lead to an increase in blood pressure, renal cell proliferation and hypertrophy, stimulation of reactive oxygen species and insulin resistance. Association of AT receptor gene polymorphisms and DM and its complications in different patient populations are investigated.

Keywords: angiotensin II, angiotensin II receptors, diabetes mellitus

Tsokeva Zh, Sokolova K, **Ganeva M**. Dietary supplements: Issues related to their legislation and safety monitoring. *Pharmacia*, 2016, 63(3):24-31 **SJR=0,115**

Abstract.

Over the last few decades, an upward trend in the use of dietary supplements has been observed worldwide. Accumulating information of health risk associated with the use of dietary supplements is the main cause of increased scientific interest in these products. As opposite to medicines, there are no regulatory requirements for preliminary data demonstrating the effectiveness and safety of dietary supplements. The legislation of dietary supplements still has many weaknesses and it is in the process of development. Clarifying the legislative and health problems associated with dietary supplements use is an important factor supporting their safe and rational use.

Keywords: dietary supplements, legislation, safety, claims

Sokolova K, Tsokeva Zh, Marinova J, **Ganeva M**. Practices regarding plant-based food supplements among outpatient care physicians. *Pharmacia*, 2018, 65(4):14-24. **SJR=0,158**

Abstract:

The increasing use of food supplements (FS), including plant-based food supplement (PBFS), raises questions about their safe use. The risk of adverse reactions (ARs) and interactions associated with FS implies the need for active communication between physicians and patients. The practice and knowledge of outpatient care physicians (OCPs) towards PBFS and its association with physicians' characteristics was examined in a cross-sectional study conducted in Stara Zagora, Bulgaria. Primary data were collected using directly administered questionnaire. More than two-thirds (89.8%) of the respondents recommended PBFS. A substantial part inquired about patient use of PBFS (76.8%) and discussed issues related to PBFS (65.7%). A moderate positive correlation was found between the personal use of PBFS and their recommendation to patients ($p < 0,001$). More than half of the OCPs (58.10%) claimed to have poor or no knowledge of PBFS. The majority emphasized the need for additional education concerning the efficacy and safety of PBFS.

Keywords: plant-based food supplements, practice, physicians

Georgiev Ts, Hadzhibozheva P, Genov N, Pashova L, Tsokeva J, Nancheva Kr, Sandeva R, Ilieva G, Tolekova A, **Ganeva M**. Metabolic disturbances in fructose fed rats and their impact on Angiotensin II stimulated contractility of the smooth muscle, *Folia Medica*, 2020, 62(4):802-811 DOI: 10.3897/folmed.62.e50410 **SJR=0. 245**

Abstract

Introduction: The high-fructose diet in rats has been reported to cause metabolic disorders such as impaired fasting glucose levels, insulin resistance, dyslipidemia, and dysregulation of the renin-angiotensin system. This could lead to further complications, for instance, to the smooth muscle dysfunction.

Aim: The present study aimed at developing fructose-induced metabolic perturbations in rats and the investigation of their impact on angiotensin II-induced smooth muscle intestinal motility.

Materials and methods: Mature Wistar rats were randomly divided into two groups (9 rats per group): control group (drinking tap water) and fructose-drinking group (15% fructose, dissolved in tap water). At the end of the experimental period (11 weeks), the plasma levels of insulin, renin, angiotensin II and creatinine, as well as the lipid profile were assessed. Morphometric analysis and lipid index calculation were

also performed. The contractile properties of ileum, colon and rectum were studied using stimulation with angiotensin II in the isolated tissue bath system.

Results: Our experiment showed that drinking 15% fructose solution induced dyslipidaemia accompanied by elevated lipid indexes as well as an increase in creatinine and renin plasma levels in the rats.

Conclusions: Fructose drinking and consequently the developed metabolic disorders modified the Ang II-induced intestinal activity causing a gradual alteration in the distal direction with the rectum being the most strongly affected organ.

Keywords: angiotensin II, fructose, intestinal dysfunction, metabolic perturbations

Hadzhibozheva P, Pashova-Stoyanova L, Tsokeva Zh, **Ganeva M**, Nancheva Kr, Ilieva G, Nanchev V, Tolekova A, Georgiev Ts. Appetite-regulating hormones in rats with fructose-induced metabolic changes *Pharmacia* (in press) **SJR₂₀₂₁=0,166**

Abstract

Objectives: The aim of this research is to examine the effects of fructose-drinking on the plasma levels of appetite-regulating hormones insulin, leptin and ghrelin in male and female rats.

Methods: Mature Wistar rats were divided as follows: two control groups - male (CM) and female (CF); two fructose-drinking groups - male (FDM) and female (FDF), received 15% fructose solution. The experiment lasted 11 weeks. At the end, insulin, leptin and ghrelin levels as well as lipid and glucose profile were assessed.

Results: Plasma concentrations of the examined hormones were elevated in fructose-drinking groups. However, in the FDM group only the leptin levels were significantly increased compared to the control. In the FDF group, all three appetite-regulating hormones showed the highest concentrations in comparison to the other groups.

Conclusion: Sex hormones may affect the appetite-regulation signals and could be a factor contributing to degree of metabolic changes caused by long-term fructose overconsumption.

Keywords: Appetite, Fructose, Ghrelin, Insulin, Leptin

Ganeva M, I Manolova, T Gancheva, I Baldaranov, J Troeva, E Hristakieva. A preliminary study of IL-5, IL-6 and IFN- gamma serum levels in patients with generalized drug eruptions. *Trakia Journal of Sciences* 2012, 10 suppl. 2;76-79. **НАЦИД**

Abstract

PURPOSE. The aim of the present study was to investigate the serum levels of IL-5, IL-6 and IFN-gamma in patients with generalized drug eruptions of various clinical patterns.

PATIENTS AND METHODS. Six patients with generalized drug eruptions and fifty one healthy subjects serving as controls were included. The causal relationship between drugs and adverse reactions was evaluated with the Naranjo algorithm. Blood samples for cytokine assay were collected at the time of the full blown rash. Commercial solid-phase sandwich enzyme immunoassay for human IL-5, IL-6 and IFN-gamma (Quantikine® from R&D Systems, Inc) was used.

RESULTS. Serum IL-5 was elevated only in one patient with DRESS syndrome. Serum IL-6 was insignificantly elevated in patients with drug eruptions compared to controls. There were no significant differences in serum IFN-gamma levels between patients and controls.

DISCUSSION. The combined investigation of cytokines in drug eruptions may contribute to a better understanding of their pathogenesis, and consequently to exact diagnosis and treatment. For definite conclusions more patient cases and repeated blood sampling are required.

Keywords: drug eruption, DRESS syndrome, IL-5, IL-6, IFN-gamma.

Ganeva M, I Manolova, T Gancheva, J Troeva, I Baldaranov, E Hristakieva. TNF- alpha serum levels in patients with adverse cutaneous drug reactions. *Trakia Journal of Sciences* 2014,12, suppl. 1:219-222. **НАЦИД**

Abstract

PURPOSE. The aim of the present study was to investigate the serum levels of TNF-alpha in patients with adverse cutaneous drug reactions (ACDRs).

PATIENTS AND METHODS. Thirteen patients with ACDRs of variable clinical presentation predominantly with maculopapular drug exanthems (MDEs) and twenty six controls were studied. In eight cases the skin eruption was accompanied by systemic symptoms. The causal relationship between drugs and adverse reactions was evaluated with the Naranjo algorithm. Commercial ELISA tests for human TNF-alpha were used.

RESULTS. The causality of ACDRs was rated as “probable” in 4 cases and as “possible” in 9 cases. The serum TNF-alpha level in the patient group was significantly elevated ($p=0.023$) in comparison with controls. There was no relationship between the presence of systemic symptoms in patients with ACDRs and serum levels of TNF-alpha above the median of the controls ($p=0.51$).

CONCLUSIONS. TNF-alpha is a versatile cytokine that could be involved in the mechanism of immediate and in T-cell mediated reactions to drugs. MDEs, the most common manifestation of ACDRs have been associated with variable T-cell populations and cytokine patterns. The elevation of serum TNFalpha in our series of patients comprising predominantly of delayed type ACDRs confirmed a Th1 cytokine pattern.

Keywords: adverse cutaneous drug reaction, TNF-alpha, maculopapular drug exanthems.

Ganeva M. Safety profile of dipeptidyl peptidase-4 inhibitors. *Trakia Journal of Sciences* (in press) **НАЦИД**

Abstract

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are oral antidiabetic agents commonly used for the treatment of type 2 diabetes mellitus. More than ten years of clinical experience with this group of drugs provides evidence of their efficacy and good tolerability especially in patients at risk of hypoglycemia. DPP-4 inhibitors act by increasing the levels of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and thus augmenting glucose-induced insulin secretion. The enzyme DPP-4 degrades plenty of substrates including chemokines, cytokines, and neuropeptides. Thus the inhibition of DPP-4 may affect many biological and pathological processes. Although rarely, DPP-4 inhibitors have been reported to induce the development of infections, heart failure, liver injury, and pancreatitis. The long-term effects of DPP-4 inhibition on the immune function are still not clarified. The close monitoring of polymorbid patients using DPP-4 inhibitors, and the reporting of possible adverse reactions associated with these drugs is warranted.

Keywords: dipeptidyl peptidase-4 inhibitors, diabetes mellitus, adverse reaction

Gancheva T, Ganeva M, Hristakieva E. Urticarial adverse drug reactions to ACE inhibitors and beta-blockers. *Trakia Journal of Sciences* (in press) **НАЦИД**

Abstract

PURPOSE. To evaluate the incidence of urticarial adverse drug reactions (ADRs) to ACE inhibitors and beta-blockers, patient demographics, drug causality, and treatment outcome.

METHODS. An epidemiological study including 154 patients with urticarial ADRs, out of a total of 3554 hospitalized patients in the Clinic of Dermatology and Venereology, for a 7-year period. ADRs were defined according to the WHO and the Naranjo algorithm was used for case drug causality assessment.

RESULTS. Urticarial ADRs were found in 4,1% of the study population (≥ 18 years), the average age was 50,2 years, and female prevalence was established. Concomitant cardiovascular diseases were found in 45,2% of the patients and 30,1% declared using ACE inhibitors and/or beta-blockers. The suspected drug was withdrawn, and alternative therapy was recommended by a cardiologist. The Naranjo algorithm showed 4,5% “definitive”, 45,5% “possible”, and 50% “probable” urticarial ADRs. Systemic antihistamines were administered to all patients and single short corticosteroid courses were added in 81,8%. Clinical recovery was achieved in 59% of the patients and improvement in 41%.

CONCLUSIONS. The need for drug therapy and hospitalization in severe cases of urticarial ADRs to ACE inhibitors and beta-blockers are factors contributing to the overall socio-economic burden of ADRs.

Keywords: urticaria, cardiovascular drugs

Tsokeva Zh, **Ganeva M**, Hristakieva E. Dietary supplements: views of patients with chronic skin diseases. *Trakia Journal of Sciences* (in press) **НАЦИД**

Abstract

Purpose: The study aims to examine the use of dietary supplements (DSs) in patients with chronic dermatological diseases, as well as the patients' views of the safety and benefit of DSs.

Methods: A cross-sectional study of patients hospitalized in the Clinic of Dermatology and Venereology at the University Hospital "Prof. Dr Stoyan Kirkovich" - Stara Zagora from March 2019 to March 2020 was performed. A specially designed and validated questionnaire was used to collect data. Descriptive statistics was performed to analyze the results.

Results: Overall 250 patients were involved in the study. The intake of DSs was established in 174 (69.6%) of the participants. Commonly used DSs were vitamins/minerals (41.2%) and herbal supplements (8.2%). Most of the respondents (59.2%) were ignorant about adverse reactions to DSs and 44.4% perceived DSs as completely safe. The majority of DSs consumers (59%) declared satisfaction with the effect of DSs and were convinced (62.4%) of their benefits.

Conclusions: DSs are widely used in patients with chronic skin diseases. Most of the patients are ignorant about the risk associated with DSs intake. Physicians' awareness of DSs use in hospitalized patients is important for the rational use of DSs and their safe combination with drugs.

Keywords: food supplements, safety perceptions, dermatology disorders

Ganeva M, T. Gancheva, I. Baldaranov, N. Kiriyaq, E. Hristakieva. Risks of oral methotrexate administration in outpatients. *Journal of biomedical and clinical research*, 2014, 7(1):59-64.

Summary

Methotrexate (MTX) is a cytostatic agent used in oncology. Because of its immunosuppressive properties, MTX is also used in autoimmune disorders. Low-dose MTX regimens in the treatment of rheumatoid arthritis and severe psoriasis are considered to be safe. However, pharmacovigilance centers warn of serious and even fatal incidents due to errors in oral MTX administration. The aim of this case series presentation was to identify the specific factors related to the development of adverse drug reactions (ADRs) induced by MTX. A prospective pharmacovigilance study was conducted at the Clinic of Dermatology, University Hospital, Stara Zagora. We report 3 cases of patients with psoriasis vulgaris in which severe haematological abnormalities associated with previous administration of MTX were detected during hospitalization. A 73-year old female with malaise, vomiting and oral ulcers who had taken approximately 120 mg MTX was found to have pancytopenia. A 59-year old male hospitalized for psoriatic erythroderma who had erroneously taken 10 mg MTX daily instead of weekly for 8 days, was diagnosed with bicytopenia and toxic hepatitis. An 88-year old male with psoriatic arthritis presented with aphthous stomatitis, erosive crusted lesions, ecchymoses and aplastic anemia 2 weeks after treatment with 12.5 mg MTX once weekly plus i.m. Movalis®, followed by Diclophenac Duo®. The main predisposing factors for the development of these ADRs were patient-related dosage errors and concomitant administration of NSAIDs. Safe use of oral MTX requires clear dosing instructions and strict patient compliance. Potential drug interactions of MTX with other drugs should also be considered.

Keywords: methotrexate, adverse drug reactions, pancytopenia

Ганчева Т,Е Христакиева Е, **М. Ганева**. Розацея. *МедикАрт - Алергология, Дерматология, Офтальмология* 2014, 2:22-23.

Розацеята (Rosacea) е релативно честа хронична фациална инфламаторна дерматоза, енигматична по отношение на етиопатогенетични хипотези. Екзантемът обикновено е центрофациален и вариабелен по морфология – телангиектатичен еритем, папуло-пустули, себацейна хиперплазия, фиброзиране. Клинично дерматозата се разделя в няколко субтипа и стадия, междукоито често има припокриване. При леките форми се предпочита локална терапия, а при тежко протичащите се добавя системна с антибиотици или ретиноиди. Необходимо е обучение на пациентите по отношение на бенигнения характер на заболяването, хронично рецидивиращото протичане, избягването на тригерите, подходящите хигиенни грижи за кожата и проложението на фотопротектори.

Христакиева Е, Т. Ганчева, **М. Ганева**, Д. Ганчева, Н. Кирияк, Ж. Троева, В. Велев. Eczema herpeticum. Сборник доклади Научна конференция за студенти и преподаватели 65 години Медицински колеж. Стратегии и иновации в развитието на медицинското образование” 19 октомври 2012. Академично издателство Тракийски университет Стара Загора 2012 ISBN 978-954-338-044-2 стр. 120-122.

Abstract

A 31-year-old male hospitalized with 1-month history of atopic dermatitis relapse with progression to erythrodermia and from 2-3 days subfebrile temperature and multiple monomorphic umbilicated vesiculopustules with erosions and crusts in evolution, localized on the face and trunk was presented. Laboratory analysis revealed elevated erythrocyte sedimentation rate and serum IgE levels. A bacterial culture swab of the facial lesions identified Staphylococcus aureus, haemocultures were negative. Skin biopsy revealed dermatitis. The precise patient diagnosis was Erythrodermia atopicum impetiginisata and Eczema herpeticum. He has been treated with Aciclovir® 5 x 800 mg p.o., Medoclav® 3x625 mg p.o. and antihistamines. Emollients and antiseptics were applied topically. Eczema herpeticum (EH), initially described by Moritz Kaposi in 1887 is a potentially life-threatening disseminated cutaneous viral infection that arises in areas of pre-existing dermatoses with defects in the barrier function and/or abnormalities in the immune system. The diagnosis of EH is mainly clinical, but can be verified by direct fluorescent antibody testing and viral culture. Tzanck smear, skin biopsy and serology are of little diagnostic value. The aetiopathogenesis, clinical presentation and management of this condition are discussed, and the importance of early recognition by the clinician is highlighted.

Keywords: Eczema herpeticum, Erythrodermia atopicum, treatment

Ганева М, Т. Ганчева, В. Велев, Е. Христакиева. Vasculitis leucocytoclastica – клиничен случай. Юбилейната конференция - 20 години специалност „Рехабилитатор” в Медицински колеж – Стара Загора 16 - 17 май 2014 г. Сборник от конференцията. Академично издателство на Тракийски университет Стара Загора 2014 ISBN 978-954-338-077-0 стр. 231-235.

РЕЗЮМЕ

Представя се пациент на 23 години, хоспитализиран по повод на фебрилитет до 38° С с давност от 1 ден, съпроводен от дисеминиран полиморфен екзантем, ангажиращ предилекционно долните крайници и флексорните части на горните, представен от петехии, екхимози, папули и везикули. Кожният обрив се предшества от гнойна ангина, лекувана амбулаторно с клиндамицин и гентамицин. Лабораторните изследвания показват ускорено СУЕ, левкоцитоза с олевяване, повишен С-реактивен протеин, ANA 1:640. Серологичните изследвания за луес, ХИВ, хронични хепатити са негативни. Антистрептолизиновият титър е под 200 ASE. Копрокултурата установява *S. albicans* - 103 /ml, чревни паразити не се демонстрират. Хистологичното изследване е с картината на левкоцитоклазичен васкулит. Уточнени са диагнозите Vasculitis leucocytoclastica, rhinotonsillopharyngitis acuta. Преустановено е приложението на всички лекарства, прилагани амбулаторно от пациента. Проведено е комбинирано лечение с H1- и H2-блокери, съдоукрепващи лекарства и антибиотик от групата на пеницилините за лечение на придружаващата инфекция на горните дихателни пътища. Прогнозата на заболяването е добра при липса на ангажиране на вътрешни органи. Идентифицирането на възможните етиологични фактори, включително лекарства,

и елиминирането им е важно с оглед не само на успешното лечение на левкоцитоклазичния васкулит, но и на профилактиката на бъдещи рецидиви.

Ключови думи: левкоцитоклазичен васкулит, етиология, лечение

Sokolova K, Tsokeva Z, **Ganeva M.** Plant-based food supplements: how do physicians perceive them? *Science & Technologies*, 2016,VI(1): 87-94

Abstract

There is an increased interest and growing use of plant-based food supplements (PBFS) among patients. In most cases, this occurs without recommendation from doctors and without doctors' knowledge. Very often PBFS are co-administered with drugs that put users at risk of adverse interactions and places professional responsibility upon doctors to establish and consult the use of PBFS.

AIM. To investigate physicians' professional opinion(s) about PBFS.

MATERIAL AND METHODS. A survey questionnaire, specifically designed for the purposes of the study, was directly administered to 108 primary care physicians. The questionnaire included a section with a 5-point Likert-type scale which established consent with 5 statements clarifying physicians' perceptions about PBFS.

RESULTS. Conviction that PBFS may have positive effect on health are found in more than half of respondents (72.2%). 62.8% of respondents perceive the natural origin of PBFS as a guarantee of their safety. An equal/identical percentage of participants (62, 9%) are aware of the possibility for interactions between PBFS and concomitantly administered drugs. The opinion that the health claims of PBFS are not always proven is shared by 66.8 % of respondents and the need for more stringent regulatory measures is supported by 73.4 %.

CONCLUSION. Physicians generally have positive attitudes towards PBFS. They realize the potential risks associated with their use and the need for more stringent regulatory requirements for these products.

Keywords: dietary supplements, attitude, perception, doctors

Ганчева Т, **Ганева М**, Христякиева Е. Уртикария - номенклатура и класификация. *Медик Арт Алергология дерматология*. 2017,7:54-56.

Уртикарията е хетерогенно, полиетиологично и полипатогенетично заболяване, характеризира се с поява на уртики и/или ангиоедем и има остро или хронично протичане. Обособена е отдавна като отделна нозологична единица, като голяма част от терминологичното многообразие има само историческо значение и понастоящем не се използва. Унифицирането на номенклатурата и класификацията на заболяването е предпоставка за прецизна диагноза и адекватно терапевтично поведение в клиничната практика, а също така и за сравняване на данни от различни клинични проучвания.

Gancheva T, Gancheva D, Troeva Zh, Velev V, Hristakieva E, Tsokeva Zh, **Ganeva M.** Carbamazepine-Induced DRESS Syndrome: A Case Report. *J Pharmacol Clin Toxicol* 2017, 5(1):1066.

Abstract

Adverse drug reactions (ADRs) induced by carbamazepine may have diverse clinical manifestations and variable severity. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, potentially life-threatening acute ADR, typically characterized by a long latency period from drug exposure. DRESS syndrome is defined by the presence of fever, cutaneous eruption, lymphadenopathy, internal organ involvement (such as hepatitis, carditis, interstitial nephritis and interstitial pneumonitis) and hematological abnormalities, mainly leucocytosis, eosinophilia and sometimes atypical lymphocytosis.

We report a clinical case of DRESS syndrome with liver injury, evaluated with the RegiSCAR scoring system as a "definite case" possibly induced by carbamazepine (CBZ) in a patient with anxiety disorder,

bronchial asthma and polyglandular autoimmune syndrome (PAS) type 3A including type 1 diabetes mellitus and autoimmune thyroiditis.

Infections, neoplastic and collagen vascular diseases were excluded. The patient was successfully treated with corticosteroids and hepatoprotectors. During a 3-month follow-up the dosage of corticosteroids was gradually tapered and stopped.

Patients on CBZ which is increasingly used as a mood stabilizer must be carefully monitored for ADRs including DRESS syndrome.

Keywords:• Carbamazepine• DRESS syndrome• Adverse drug reaction

Ганчева ТТ, Ганева МГ, Велев ВА, Ганчева ДД, Троева ЖТ, Мануелян К, Дърленски РБ, Христатијева ЕХ. Telangiectasia macularis eruptiva perstans linearis unilateralis. *Дерматология и Венерология* 2017, 1:10-13.

Резюме

Мастоцитозата е хетерогенна група от редки заболявания. Клиничният спектър варира от относително доброкачествени форми с изолирана кожна локализация до много агресивни форми с екстензивно системно ангажиране и лоша прогноза. Представен е клиничен случай на болна с изключително рядка кожна форма на telangiectasia macularis eruptiva perstans (ТМЕР) с линеарен унилатерален екзантем.

Ключови думи: telangiectasia macularis eruptiva perstans, mastocytosis

Ганчева Т, Мануелян К, Лавчева Р, Ганева М, Делийска Р, Ганчева Д, Христатијева Е. Адалимумаб в терапията на псориазис и гноен хидраденит. *Медикарт: Алергология, Дерматология, Офталмология* 2018, 2:37-40.

Резюме

Псориазисът и гнойният хидраденит са социално значими възпалителни заболявания с хронично-рецидивиращ ход. TNF- α инхибиторите принадлежат към групата на биологичните лекарства, които действат специфично чрез таргетирано потискане на важни патогенетични компоненти на възпалителния процес. Адалимумаб е TNF- α инхибитор с висока ефективност, който играе важна роля в съвременната терапия на умерен и тежък псориазис при неуспех или противопоказания за прилагането на класическите методи за лечение (фототерапия, системни ретиноиди и неспецифични имunosупресори като метотрексат

и циклоспорин). Целта на лечението е да се сведе до минимум тежестта на симптомите, да се осигури продължителен безопасен контрол на заболяването и да се подобри качеството на живот на пациента. При много тежки форми на гноен хидраденит, адалимумаб намалява локалното възпаление, поради което може да се използва и в предоперативния период, преди радикална хирургична ексцизия на обхванатите от патологичния процес области.

Ганчева Т, Мануелян К, Ганева М, Делийска Р, Дърленски Р, Христатијева Е. Дерматопороза. *Медикарт: Алергология, Дерматология, Офталмология*, 2018, 8:34-36.

Резюме

Дерматопорозата е относително нов термин, предложен за описване на синдрома на хроничната кожна инсуфициенция. Заболяването има мултифакторна генеза и се характеризира с повишена ранимост на кожата. Дерматопорозата може да бъде първична и вторична. Екзантемът е локализиран предимно по екстензорните повърхности на предмишниците и подбедриците, както и по гърба на ръцете, в престерналната област и скалпа. Морфологичните белези на заболяването включват кожна атрофия, сенилна пурпура, хиперпигментации, псевдоцикатрикси, кожни лацерации и дълбоки дисекиращи хематоми без или със некроза. Познаването на рисковите фактори и на клиничните симптоми в съответните стадии на дерматопорозата е предпоставка за адекватно терапевтично поведение и подходящи превантивни мерки.

Ганчева Т, Делийска Р, Мануелян К, **Ганева М**, Дърленски Р, Христкаева Е. Себорейен дерматит при възрастни. *Medinfo. Алергология, дерматология, онкология, хематология*, 2019,4:58-61.

Резюме

Себорейният дерматит (СД) е честа хронична еритемо-сквамозна дерматоза, засягаща предимно кърмачета и възрастни. Има недобре изяснена мултифакторна етиопатогенеза. Екзантемът е локализиран предимно в себорейните зони на кожата. Описани са различни клинични форми на СД в зависимост от възрастта, морфологията, локализацията и тежестта на заболяването. Познаването на предразполагащите екзогенни и ендогенни фактори, както и на клиничните форми на СД, е предпоставка за провеждане на адекватна терапия и профилактика.

Цокева Ж, Александрова Е, **Ганева М**. Генетични фактори, полияващи нивата на серумния витамин Д. *Science and technologies*, 2021, XI, (1) *Medical Biology Studies, Clinical Studies, Social Medicine And Health Care* 97-103.

Abstract

Vitamin D is a prohormone involved in many biological processes. In addition to the main effect of vitamin D on calcium-phosphorus metabolism there is growing evidence of its immunomodulatory effect, as well as effects on cell proliferation, differentiation and apoptosis. A link has been established between serum vitamin D levels and the development of some systemic diseases. Vitamin D deficiency has been established in autoimmune diseases, malignancies, cardiovascular and metabolic disorders. The serum concentration of vitamin D depends largely on some external factors such as diet, skin type, geographical latitude, which partly explain the interindividual differences in vitamin D status. Genetic polymorphisms, mainly related to its metabolism, are important for the concentration of vitamin D. Polymorphic variants of genes involved in cholesterol synthesis (DHCR7), hydroxylation (CYP2R1, CYP27B1, CYP24A1), vitamin D transport (GC) and vitamin D receptor (VDR) have been described. Polymorphisms of CYP2R1 and GC genes appear to be the most important. The polymorphisms rs10741657 and rs10766197 of the CYP2R1 as well as rs7041 and rs4588 of the GC genes are functional and the genotype may determine a low concentration of vitamin D. Knowledge of genetic determinants of human vitamin D status contributes to the elucidation of the pathogenesis of a number of diseases and to the identification of at-risk population. Genetic polymorphisms can explain both population differences in vitamin D levels and variations in the individual response to vitamin D supplementation.

Keywords: vitamin D deficiency, genetic polymorphisms

Ганчева Т, **Ганева М**, Христкаева Е. Уртикария – дефиниция, номенклатура и класификация. *Дерматология и венерология*, 2022, 2:8-14.

Резюме

Уртикарията е заболяване, което може да засегне всички възрастови групи, и е едно от най-честите в специализираната практика на дерматолози, алерголози, педиатри, лекарите по обща медицина и в спешната медицина. Унифицирането на номенклатурата и класификацията на заболяването е предпоставка за прецизна диагноза, адекватно терапевтично поведение, а също така и за сравняване на данни от различни клинични проучвания и от национални регистри.

Ключови думи: уртикария, класификация