

assessment (RA), which involves examining the intrinsic toxicity of an agent (hazard assessment) and comparing it with the anticipated human exposure to characterize the likelihood of adverse effects (risk characterization). Although this process is meant to integrate all data sources (human, environmental, in vivo, in vitro, in silico), in practice existing regulations of pharmaceutical and chemical substances continue to ask for sector-specific RAs, each of which has its own specific information requirements and uses different methods for the ultimate risk quantification. Although regulators often stress the primacy of human data, in practice their use is constrained by availability and lack of defined quality criteria. There have been some efforts in the past to develop frameworks for the use of human data (eg, from poison centers) for risk assessment purposes. However, these have had only limited success. More recently, integrated approaches have been developed using information from animal studies and human data based on mode of action and weight of evidence concepts. These approaches need to be tested and validated. Harmonized data collection based on defined quality criteria is a precondition for better use of human data in risk assessment. It will only become a reality if existing networks of institutions such as poison control and clinical toxicology centers are being strengthened and, importantly, if they interact with regulatory decision makers on a regular basis. This will result in enhanced sharing of knowledge, build consensus, and facilitate clear, easily understood, transparent, and unambiguous integrated RA procedures. Network initiatives such as the EU FP7 project HEROIC aim to contribute to the development of such harmonized approaches that meet the challenges of RA.

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## HISTORICAL DEVELOPMENT AND CURRENT STATE OF CLINICAL PHARMACOLOGY IN RUSSIA

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**Summary:** K. Zagorodnikova, A. Burbello, M. Frolov, D. Sychev, V. Petrov

Clinical pharmacology in Russia was established 13 years after the first World Health Organization (WHO) manifesto describing its duties was released. In 1983, it was defined as a separate educational discipline in medical universities. Starting from 1997, the medical specialty “clinical pharmacologist” was established, and its functions were defined. It was built on the union of pharmacology and internal medicine, and that is why clinical pharmacology in Russia is characterized by close proximity to routine patient care. A clinical pharmacologist in Russia should first receive training in internal medicine and then 2-year specialization in clinical pharmacology. The current main duties of clinical pharmacologists in Russia are defined by the ministerial laws released in 2003 and 2010, updated in 2012. According to these documents, clinical pharmacologists should see patients and be able to adjust treatment by taking into account various possible factors of individual response to medications. They should advise when necessary and interpret results of pharmacogenetic analyses; perform therapeutic drug monitoring and drug interaction analyses; and diagnose, register, and manage adverse drug reactions. Furthermore, clinical pharmacologists should manage quality control of medications used in their hospitals, participate in drug and therapeutics committees, develop and maintain a system of formulary lists of medications, perform drug utilization surveillance, participate in microbiology monitoring in relation to antibiotic utilization, define economic feasibility of different medications use, and approve purchase of drugs according to the general hospital needs.

They should also provide informational services to physicians and patients on various issues of rational drug use.

According to the current law, every medical institution should have a position of clinical pharmacologist; hospitals with >500 beds are advised to have a corresponding division. This provides grounds for active development of the specialty and improvement of educational programs. Some universities have courses of clinical pharmacology included in the curriculum of other specialists. Since 2009, clinical pharmacologists in Russia are cooperating within the all-Russian “Association of Clinical Pharmacologists” comprising the vast majority of regions. The association is performing important organizational, informational and expert functions.

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## DIABETES, DIABETES RISK FACTORS AND TREATMENTS, AND BREAST CANCER

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**Summary:** To clarify the potential association between diabetes, related factors, treatments, and breast cancer risk, a series of meta-analyses was carried out following PRISMA guidelines. For breast cancer at all ages, the risks obtained from prospective studies were: diabetes (SRR = 1.27 [95% CI, 1.16 to 1.39]); physical activity (SRR = 0.88 [0.85 to 0.92]); glycemic load (SRR = 1.05 [1.00 to 1.10]); glycemic index (SRR = 1.05 [1.00 to 1.09]); fasting glucose (SRR = 1.14 [0.94 to 1.37]); serum insulin (SRR = 1.11 [0.75 to 1.85]); c-peptide (SRR = 1.00 [0.69 to 1.46]), and adiponectin (SRR = 1.16 [0.93 to 1.46]). An increase of 5 units in BMI was associated with postmenopausal breast cancer (SRR = 1.12 [95% CI, 1.08 to 1.16]) but not at premenopausal ages (SRR = 0.83 [95% CI, 0.72 to 0.95]). Serum insulin and c-peptide were associated with breast cancer at postmenopausal ages but not at premenopausal. For IGF-1, Hodge's standardized mean difference (HSMD) was calculated, and there was no significant association with breast cancer (HSMD = 0.026 [95% CI, -0.031 to 0.084]).

The SRR for breast cancer among users of insulin glargine was 1.08 (0.98 to 1.20) and was 0.92 (0.32 to 2.65) when restricted to randomized trials. Among new users, the SRR for breast cancer was 1.09 (0.98, 1.21), and there was no trend of increasing breast cancer risk with increasing duration of use of glargine ( $\beta = 0.04$ ) ( $P = 0.52$ ). Risk of breast cancer in a prospective cohort declined with increasing follow-up, from 1.99 (1.31, 2.03) with 2 years of follow-up, to 1.60 (1.10 to 2.32) with 3 years, 1.50 (1.10 to 2.10) with 4 years and 1.18 (0.84 to 1.66) with 5 years of follow-up. There is no reduction in risk of breast cancer associated with metformin use (SRR = 0.96 [95% CI, 0.85 to 1.08]) even for the longest duration of use (SRR = 0.94 [95% CI, 0.81 to 1.09]).

An association between these 2 common diseases could have important implications for public health, with common risk factors

driving further increases in both diseases yet holding the tantalizing possibility for prevention of both.

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### INTERFERON ALPHA AND POSTERIOR UVEITIS

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**Summary:** Noninfectious uveitis is a sight-threatening, immune-mediated intraocular inflammatory disorder. Posterior uveitis can involve the retina, choroid, vitreous, and optic nerve. Uveitis can result from heterogeneous numerous etiologies, including infectious, autoimmune causes, and tumoral-mimicking uveitis. Infectious and tumoral causes need specific treatment. Primary or secondary autoimmune disorders of posterior ocular segment require anti-inflammatory treatment to prevent from visual loss.

Uveitis is responsible for ~10% of the visual handicap.

Immunodepressive treatment is required in sight-threatening noninfectious posterior uveitis. Nowadays, corticosteroid therapy remains the first-line conventional treatment for active, noninfectious uveitis. Corticosteroids could be administered by peri or intra-ocular injection, using intravitreal implant, or systemically. The limit of intra-ocular steroid are side effects as secondary glaucoma and a short time therapeutic activity needing re-injection or bilateral injection for bilateral chronic uveitis. Therefore, posterior chronic bilateral uveitis is still nowadays treated with an oral steroid such as prednisone. If the daily dose threshold is greater than ~0.2 mg/kg/d of prednisone, a combination of immunosuppressive or immu-

nomodulator drugs is indicated, both for their own immunosuppressive and steroid-sparing capabilities.

Immunosuppressive agents, conventionally used in its indication, can be categorized into 3 main classes: T-cell inhibitors (cyclosporine, tacrolimus), antimetabolites (azathioprine, methotrexate, mycophenolate mofetil, leflunomide), and alkylating agents (cyclophosphamide, chlorambucil). All had been shown efficient in severe uveitis. Side effects include increased risk of infection, hematologic toxicity, sterility, and secondary malignancy. Moreover, immunosuppressive drugs can exhibit selective tissue toxicity as renal toxicity induced by cyclosporine treatment.

The risk of severe side effects of immunosuppressive drugs has led to the evaluation of the therapeutic benefit of immunomodulator drugs such as polyclonal antibodies and interferon alpha. The therapeutic benefit of INF $\alpha$  in Behcet's disease was recently documented in a meta-analysis of both systemic disease control and uveitis control. The frequency of ocular attacks was significantly reduced compared with the pretreatment observation period, and there was a significant steroid-sparing effect. A randomized prospective study has been done using 3 arms - with only steroids systemic therapy - with only inf alpha systemic therapy - under only observation, for 4 months, in the chronic noninfectious posterior uveitis associated to macular edema. The main criteria was the central foveal thickness, an objective, reproducible parameter measured through optical coherence tomography, a noninvasive tool. The results will be presented in the conference.

*Trial Randomized multicentric trial. Code number P051032. Biomedical research Phase II with individual direct benefit.. Promotor: Assistance Publique des Hôpitaux de Paris.*

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