ments. However, these drugs show slow onset of action and limited efficacy, making necessary the use of drug augmentation strategies or more aggressive interventions. Two important observations have emerged in recent years indicating that more rapid and effective antidepressant treatments are possible. On the one hand, the deep brain stimulation (DBS) of ventral anterior (subgenual) cingulate cortex (Cg25) evokes rapid mood improvements in subgroups of treatment-resistant depressive patients, likely mediated by a functional remodeling of cortico-limbic circuits. On the other hand, the noncompetitive NDMA receptor antagonist ketamine can also evoke raid (eg, 2 hours) and persistent (up to 1 week) improvements in some treatment-resistant patients. Moreover, recent preclinical observations indicate the antidepressant capacity of nGluR agents. Overall, this supports the usefulness of glutamatergic transmission as a new area in antidepressant drug development. On the monoamine side, new preclinical and clinical research should clarify the different roles played by 5-HT receptors in depression as well as the brain areas and circuits responsible for therapeutic improvement. This will lead to the synthesis of new agents blocking the serotonin (and possibly norepinephrine) transporter, which will also activate or block 5-HT receptors playing, respectively, positive (eg, postsynaptic 5-HT1A, 5-HT4) or negative (eg, presynaptic 5-HT1A,/1B, 5-HT2A, 5-HT2C,5-HT3) roles in antidepressant effects.

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LIPID EMULSION AS A NEW ANTIDOTE—CURRENT USE, EXTENSION FROM LIPOPHILIC LOCAL ANESTHETICS TO OTHER DRUGS, AND STATE OF THE ART

T. Bania*

Emergency Medicine, St. Luke's-Roosevelt/Columbia University, New York, New York

Summary: Intravenous fat emulsion (IFE) has been used as an antidote and is most extensively studied for the treatment of local anesthetic toxicity. New applications beyond local anesthetic are proposed, including calcium channel blockers, cyclic antidepressants, clomipramine, and β-adrenergic antagonists. There are 3 proposed mechanisms of action of IFE in toxicology: modulation of intracellular metabolism, a lipid sink or sponge mechanism, and activation of ion channels. The lipid sink/sponge model is the most likely mechanism. Several experimental models demonstrate the benefit of IFE in bupivacaine, calcium channel blockers, cyclic antidepressants, and β-adrenergic antagonist toxicity. Multiple case reports using IFE in a variety of drug toxicity report improvement. Potential adverse effects may limit use but have been reported infrequently, and the benefit of IFE may outweigh potential risks. The dose, timing of administration, and the uses and comparison with other treatments are in need of future studies. The recommended dose of 20% IFE is a 1.5-mL/kg bolus followed by 0.25 mL/kg/min or 15 mL/kg/h to run for 30 to 60 minutes. The bolus can be repeated several times for persistent asystole, and the infusion rate can be increased if blood pressure decreases.

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CHALLENGES IN PARACETAMOL POISONING

N. Bateman*

NPIS Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Summary: Paracetamol poisoning was first reported >45 years ago, but its optimum management is still a matter of debate. In part this is because of the difficulty in precise risk stratification early in poisoning and a lack of effective antidotal treatments for those who present late after ingestion. National drug regulatory and poisons information systems in different countries provide different advice, and the United Kingdom changed its risk stratification advice in 2012 after >30 years. Observational data suggest that repeated ingestions of lower doses may cause more severe liver damage than a single ingestion, but the reasons for this remain unclear. The antidote IV acetylcysteine is given in a complex dose regimen that is not tailored to the amount of toxin ingested, and the initial duration of antidote therapy was determined empirically in the mid-1970s. Adverse effects to the antidote acetylcysteine are a further challenge, as they are more frequent at lower paracetamol concentrations.

We have recently been able to establish a population estimate of risk, which shows that early presentation managed conventionally results in good outcome and that mortality is almost always in those presenting >15 hours after first ingestion. Co-ingestion of other drugs that delay gastric motility and the introduction of modified-release paracetamol products further complicate management approaches, and the safety of marketing of SR preparations must be questioned from a public health perspective. New biomarkers offer the potential to better identify patients who are at specific risk, and appear to precede, and better predict, than rises in the traditional transaminases. Newer, modified acetylcysteine regimens should improve its safety profile. Linked to new biomarkers, these potentially offer shorter durations of hospital stay for paracetamol overdose.

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NEW DEVELOPMENTS IN THE TREATMENT OF INBORN ERRORS OF METABOLISM

M.R. Baumgartner*

Division of Metabolism, University Children's Hospital and Children's Research Center, Zurich, Switzerland

Summary: Progress in the treatment of inborn errors of metabolism has derived from insight into their causes and has focused on nutritional limitation of a substrate or replacement of missing products, the removal of toxic metabolites and maximizing anabolism, or compensatory expression of a protein whose deficiency causes disease through stem cell or organ transplantation.

The knowledge of the biochemistry and the pathway of lysosomal enzymes and the concept of systemic delivery of a deficient enzyme carrying a mannose-6-phosphate residue that serves as recognition marker for both uptake and transport to lysosomes resulted in the first successful enzyme replacement therapies in patients with lysosomal storage disorders.

The use of small molecules as therapeutic agents is another approach that is being applied widely to inborn errors of metabolism. This is illustrated by substrate reduction therapy, which has shown to be effective in some lysosomal storage disorders and complements some of the limitations of enzyme-replacement therapy (eg, crossing the blood-brain barrier). Pharmacologic chaperones generally bind directly to mutant proteins and mediate improvement in the folding, the transport, or the stability and hence elevated levels of mutant protein with residual function. One example for this is treatment with pharmacologic doses of cofactor or cofactor analogues such as in phenylketonuria. Other novel therapeutic approaches include the use of "old" approved drugs to compensate for functional deficits or antagonize unwanted effects. One example is the use of losartan to reduce TGF-b activity in Marfan's syndrome and other genetically caused forms of aortic aneurysm.

Finally, new developments will be discussed such as manipulation of gene expression by suppression of nonsense-mediated decay or manipulation of pre-mRNA splicing using short oligonucleotides.

These include siRNA and microRNA used to degrade mRNA transcripts and suppress protein translation, and antisense oligonucleotides used to manipulate splicing.
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PHARMACOGENETICS AND OTHER FACTORS IN INDIVIDUALIZATION OF ORAL ANTI-VITAMINE K ANTI-COAGULANTS

P. Beaune*
Université Paris-Descartes, Paris, France
Summary: The use of vitamin K antagonists (VKA) is challenging because of their narrow therapeutic index and a large interindividual variability. Pauci data were available regarding the relative contribution of pharmacogenetic and nongenetic factors to VKA response in specific populations (elderly, children, resistant patients). In 2 cohorts of elderly patients receiving warfarin (n = 300) or fluindione (n = 156), genetic factors were the main determinants of the maintenance dose, explaining ~20% of the variability versus ~10% for nongenetic factors. The variables significantly associated with the maintenance dose were VKORC1/CYP2C9/CYP4F2/EPHX1 and age for warfarin, and VKORC1/ABCB/CYP4F2, weight, and amiodarone intake for fluindione by multivariate analysis. During warfarin initiation, VKORC1 genotype had a strong predictive value for warfarin sensitivity. When building prediction models of the warfarin dose, VKORC1/CYP2C9 were the best predictors before initiation, whereas their contribution was negligible once INR value was available after starting warfarin using a standardized regimen.

In the children cohort (n = 120), height and VKORC1/CYP2C9 were the main determinants of warfarin dose requirement, explaining 70% of the variability accounting for 48% and 20%, respectively.

Among the 100 patients resistant referred to us for analysis, only 30 patients were carriers of VKORC1 mutations for which in vitro functional characterization was performed. Our results suggest the involvement of other genetic factors in VKA resistance.

Pharmacogenetics will help the development of personalized medicine to improve safety and efficacy during VKA treatment. Whether genetic testing improves long-term anticoagulation control in patients receiving VKA and prone to instability remains to be determined.
Disclosure of Interest: None declared.

PUBLIC HEALTH GENOMICS AND PERSONALIZED HEALTHCARE

A. Brand*
Institute for Public Health Genomics (IPHG), Maastricht University, Maastricht, the Netherlands
Summary: Rapid scientific advances and tools in genomics such as in the light of epigenomics, microbiomics, and systems biology supported by new ICT solutions not only contribute to the understanding of disease mechanisms but also provide the option of new promising applications in human health management during the whole life-course. What was a little time ago a vision for a new era of public health, in which advances from the -omic sciences would be integrated into strategies aiming at benefiting population health, is now responding to the very pressing need for the development of effective personalized health care, going even beyond personalized medicine based on a systems medicine approach. Although the utility of most genetic tests and biomarkers is still not evidence based, the real take-home message stops here and is a different one. In the personalized medicine setting, the traditional assessment and evaluation tools just do not work anymore. Thus, we clearly face the need for a new paradigm moving from population health to personal health. The paradigm shift depends on the willingness to restructure policies, and there is a clear urgency to prepare health care systems and policy makers in time.

So far, all stakeholders, including policy makers and the private sector, are struggling to translate the emerging knowledge into public health. Public Health Genomics (PHG) is the area of public health ensuring that scientific advances in genomics ("from cell...") triggered by innovative technologies are timely, effectively, and responsibly translated into health policies and practice for the benefit of population health ("...to society"). The implementation of PHG requires increased concerted activities. The Institute for Public Health Genomics (IPHG) at Maastricht University aims to fulfill this task in all European Member States by hosting the European Centre for Public Health Genomics (ECPHG) and coordinating the Public Health Genomics European Network (PHGEN). Furthermore, it closely collaborates with the European Science Foundation (ESF Forward Look on Personalised Medicine), the European Alliance for Personalised Medicine (EAPM), and the European Flagship Pilot ITFoM on the future of medicine, being one of the most ambitious worldwide, large-scale, science-driven, research initiatives that aim to achieve the visionary goal of the "virtual human."
Disclosure of Interest: None declared.

A SYSTEMATIC FOLLOW-UP OF STUDENT-PRESCRIBERS (TRACK): THERAPEUTIC KNOWLEDGE, SKILLS/COMPETENCIES AND ATTITUDE

D. Brinkman*
Clinical Pharmacology & Pharmacy, VU University Medical Center, Amsterdam, the Netherlands
Summary: One of the core objectives of medical curricula is to provide graduates with a sufficient level of therapeutic knowledge and skills. Over the last decade, a lot has changed when it comes to teaching medical students how to prescribe rationally. In the Netherlands, most medical curricula shifted from a so-called problem-based learning to a context-learning pharmacotherapy program. However, there is still no systematic approach available for assessing students' therapeutic knowledge and skills during such a context-learning curriculum. Research on this topic consists almost exclusively of descriptive and evaluative studies on different assessment methods. These studies show that the often-used single-shot assessments have their shortcomings and poorly meet the recent developments in medical education (context-learning). What is needed is a systematic approach to assessment.

In this session, David Brinkman proposes a new systematic model (*TRACK*) for assessing students' therapeutic knowledge, skills/competencies, and attitude during a context-learning curriculum. This longitudinal model is based on a set of assessment principles that are interpreted from empirical evidence. He discusses a number of challenges and opportunities around the proposed model and presents preliminary findings of this new project. One of its prime virtues is that it enables therapeutic assessment toward an assessment design that is underpinned by empirically grounded theory and, moreover, carefully follows students until they are prescribers.
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STRATEGIES FOR THE DEVELOPMENT OF TDM FOR TARGETED ANTICANCER AGENTS

T. Buclin*
Division of Clinical Pharmacology, University Hospital Center of Lausanne (CHUV), Lausanne, Switzerland