STUDYING TERATOGENIC EFFECTS OF MEDICATION USE DURING PREGNANCY: CHALLENGES AND PITFALLS

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Summary: Depending on the data sources used and the types of studies included, 29% to 99% of pregnant women in developed countries take at least 1 prescribed drug. Although some drugs, such as thalidomide and isotretinoin, are classical examples of human teratogens (nongenetic risk factors that cause birth defects), the human teratogenic risks are undetermined for >90% of prescription drug treatments approved for marketing in the United States since 1980. Due to this lack of information, adherence to pharmacologic treatment may be discouraged, which may endanger maternal and fetal health, or women may choose to terminate their wanted pregnancies based on fear of adverse effects. In other pregnancies, fetal development may be disturbed by unknown teratogenic exposures that could have been avoided. Therefore, high-quality human studies focusing on the adverse effects of medication use during pregnancy are urgently needed. However, apart from the general methodologic problems in epidemiologic research, such as confounding, selection and information bias, and limitations in making causal inferences, pharmacoepidemiologic studies focusing on birth defects face some important problems that are unique to this area of research. During this lecture, these problems and some new initiatives in epidemiologic research on adverse effects of medication use during pregnancy will be discussed.
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PREDICTION OF PHARMACOLOGICAL EFFECTS OF CNS-ACTIVE AGENTS DURING EARLY PHASES OF DRUG DEVELOPMENT

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Summary: In the last decades, several drugs for neuropsychiatric indication failed in late stages of development or were withdrawn shortly after launch, including disease-modifying compounds for dementia (eg, the γ-secretase inhibitor tarenflurbil) and innovative drugs for smoking addiction (eg, the CB1-antagonist rimonabant). A few years ago, some of the larger pharmaceutical industries decided that the financial risk of developing drugs for psychiatric indications was too large, and many CNS projects were abandoned. Currently, the industry tries to innovate CNS drug development by investing in partnerships with expert groups and exploring novel science-driven approaches. An essential requirement for a successful drug is that it reaches its therapeutic target in the right concentrations during the correct time period, and that it avoids levels or targets associated with adverse events. In addition, the drug's mechanism of action needs to have a beneficial effect on the pathogenesis or pathophysiology of the disease. Most of these aspects can be accurately determined in healthy subjects, in the earliest phases of drug development. To some extent this also includes indications of therapeutic benefit, because many diseases involve well-known physiological processes that are also measurable in normal subjects, although therapeutic benefit can only be reliably examined in patients. Thus, the predictions of the optimal dosing regimen (or the likeliness of failure) of a new drug in patients can be significantly enhanced by demonstration of optimal pharmacologic activity in every early (and later) study during drug development. This lecture will provide several examples, in which pharmacologic effect measurements were incorporated into "traditional" single and multiple ascending dose studies in Phase I. These instruments include (but are not limited to) validated effect biomarkers such as the NeuroCart CNS test battery (pharmacologic activity and beneficial/detrimental effects), PET measurements or continuous CSF-sampling (BBB-penetration), pharmacologic challenge tests (pharmacologic activity) or informative positive controls (benchmarking), and pharmacokinetic/dynamic analysis for data integration. The examples involve innovative compounds such as partial GABA-A-agonists and CB1-antagonists, and the first human studies with a fast-dissociating D2-antagonist and an orexin half-antagonist. In most of these cases, traditional approaches were misleading, but a goal-directed "question-based" application of pharmacologic tools in healthy subjects demonstrated brain penetration and meaningful functional effects (indicative of therapeutic or detrimental activity), which contributed to accurate predictions of therapeutic windows in clinical trials.
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INDUSTRY IS MORE FIT FOR CLINICAL TRIALS THAN ACADEMY

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Summary: Drug R&D is costly, time-consuming, and has a low success rate. The costs exceed 1 billion USD. From the human Phase I trial on, the increase is exponential. In the EU, 60% of clinical trials applied for every year are sponsored by the pharmaceutical industry and 40% by other stakeholders, such as academics. It is no wonder, then, that the EU Clinical Trials Directive 2011/20/EC incented protest mainly from the academic and SME stakeholders. According to the EC, although the Directive brought about important improvements in the safety and ethical soundness of clinical trials and in the reliability of clinical trials data, on the other hand, it led to the fall of the number of applications by 25%. The costs have increased. The staff needs for industry sponsors to handle the clinical trial authorization process have doubled, with SMEs facing an even sharper increase. For noncommercial sponsors, the increase in administrative requirements has led to a 98% increase in administrative costs. Insurance fees have increased by 800% for industry sponsors. Although the EC is now about to ease the burdens, it is clear that significant resources would be required anyhow. The proper and time-conscious conduct of extended, multinational, cross-continental clinical studies requires sufficient high-quality staff, logistics, experience, and knowledge of different regulatory aspects, let alone a sound financial background. This can be handled only by the help of industry resources at the end. Trends and data underpinning this opinion will be demonstrated in the presentation.
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COLLECTION AND IMPACT OF PATIENT REPORTED OUTCOMES

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Summary: The efficacy assessment in clinical studies evaluating drug effects, or more generally disease management, is generally focused on the occurrence of objective clinical or economical outcomes, in line with regulatory guidelines. However, there is growing recognition of the value of capturing wider effects of treatments reported by patients in the form of patient-reported outcomes (PROs). A PRO is defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. After examining the reasons explaining the development of these new clinical research