PSY-PGx: a new intervention for the implementation of pharmacogenetics in psychiatry

A recent Forum in this journal[1] highlighted the limited progress of pharmacotherapy in psychiatry, implying that new treatment strategies are urgently needed alongside the development of new drugs to improve patient care.

Individualizing treatment with established medications is one possible approach to significantly reduce the burden and health care costs per patient. Today, only about one third of patients attending psychiatric facilities respond fully to treatment with the available arsenal of medications[2,3]. The selection and dosing of these medications is based on a trial-and-error approach that relies primarily on the psychiatrist's experience and the patient's perception of the occurrence and intensity of side effects or clinical effects[2,3]. It can take weeks or even longer to find a medication that is sufficiently tolerable and effective for that patient[2,3].

Pharmacogenetic testing can improve this process by identifying individual-specific genetic variants that affect drug-metabolizing enzymes, drug transporters or drug targets[4-6]. In addition, genotype-dependent dosing guidelines for psychotropic drugs are available to physicians[5].

While an abundance of commercially available tests may suggest that pharmacogenetic approaches are a well-established tool in psychiatry, backed by a host of robust studies, this is not the case. The global psychiatric community still lacks an awareness and thorough understanding of the subject. Moreover, there is an urgent need for international, large-scale, independent clinical trials that can quantify and firmly establish the clinical benefits of the pharmacogenetic approach and subsequently enable further development in this area.

The European Union-funded and researcher-initiated PSY-PGx project was launched in 2021 (https://cordis.europa.eu/project/id/945151). It is the largest non-industry-funded project to implement pharmacogenetics in clinical psychiatry.

The project applies machine learning to data of already available biobanks, i.e. the Finnish hospital-based Auria Biobank (https://www.auria.fi/biopankki/sv/tutkijoille/fingenious.php) and the population-based UK Biobank (https://www.ukbiobank.ac.uk), aiming to assess the relationship between pharmacogenomics and clinical outcomes in patients with psychiatric disorders[6]. A medication prescription algorithm will be derived from these data.

Moreover, a clinical study is being conducted comparing individualized medication prescription based on pharmacogenetics to standard trial-and-error approaches. A comprehensive phenotyping and genotyping, utilizing a genome-wide microarray specifically designed with specialized pharmacogenetic content, is being performed[7]. Importantly, patients with mood, anxiety and psychotic disorders are being included. Phenotyping patients during the clinical trial aims to uncover additional genomic and environmental influences on individual medication response, incorporating passive behavioral monitoring through smartphones (https://www.behapp.com).

Patients from clinical sites across seven countries are being recruited and randomly assigned to either a pharmacogenetic group or a dosing-as-usual group, undergoing a 24-week treatment with four follow-up visits. The primary outcome focuses on personal recovery, assessed through the self-reported Recovery Assessment Scale (RAS-DS)[8]. Recent trends in psychiatric research highlight the importance of recognizing patients' personal experiences as essential outcomes and recovery indicators, complementing clinical recovery as assessed by clinicians using psychometric tools. While both dimensions are pertinent, personal recovery emphasizes the patient-centred perspective and the importance of having a good quality of life, which may be distinct from clinical improvement.

Secondary outcomes encompass measures related to treatment efficacy and tolerability, coupled with digital monitoring facilitated by the BeHapp application, which passively monitors proxies of patients' well-being and daily social functioning via their mobile phones, generating valuable longitudinal and quantitative real-world data[9]. Patient characteristics, including sex, age, comorbidity, comedication, and additional phenotypes, will be examined as covariates to assess their impact on treatment outcomes.

Furthermore, machine learning will be harnessed to scrutinize the collected data, identifying characteristics that influence medication responses. The aim is to optimize medication and dosage selection for individual patients. The collected data will be made available for re-use, facilitating further (pharmaco-)genomic research.

PSY-PGx stands as an initiative firmly grounded in rigorous adherence to good clinical and research practices. It leverages a diverse network of genomic researchers and health professionals across various disciplines. Our collaborative efforts are backed by important organizations such as the European College of Neuropsychopharmacology (ECNP), the International Society of Psychiatric Genetics (ISPG), the WPA (project participant), and the Global Alliance of Mental Illness Advocacy Networks Europe (GAMIAN, project participant).

Despite the huge potential of pharmacogenetic approaches, most countries have yet to incorporate them into routine clinical practices. Progress has been hindered by unwarranted optimism and overstated claims. Aligned with the genetic testing statement by the ISPG (https://ispg.net/genetic-testing-statement), PSY-PGx pioneers a novel model aimed at personalizing medication prescriptions. This approach involves the utilization of federated learning, also known as collaborative learning, to develop the algorithm. By employing a decentralized training method for machine learning models, the need for exchanging data across various servers is eliminated. Raw data on edge devices are thus locally utilized to train the model, ensuring enhanced data privacy.

The envisioned outcome of this initiative is a groundbreaking

pharmacogenetic algorithm that is anticipated to become an integral component of the treatment decision-making process in psychiatric practice. This algorithm has the potential to significantly enhance the effectiveness, tolerability and safety of pharmacological treatments in psychiatry. Consequently, it can enhance treatment adherence, improve overall quality of life, and contribute to the reduction of health care costs. The resulting medication prescription algorithm, coupled with a Creative Commons License model, will be made publicly available, ensuring maximum societal benefit.

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