Rev Psiquiatr Salud Ment (Barc.). 2019;12(3):135–140

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental

EDITORIAL

One decade of the first episodes project (PEPs): Advancing towards a precision psychiatry

Una década del proyecto de primeros episodios (PEPs): Avanzando hacia una psiquiatría de precisión

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First-episode psychosis (FEP) [NT: PEP in this article, for the term in Spanish: *primer episodio psicótico*] represents one of the main challenges for mental health research[1] and poses many uncertainties and unmet needs in their care. Without an appropriate differential diagnosis and early intervention, clinical development after PEP can lead to a chronic condition of varied signs and symptoms. This can greatly reduce the quality of life of the patients and their families, as well as involve a high cost for society.[1–3]

In the framework of the establishment of the Centre for Biomedical Research in Mental Health Network (Spanish acronym, *CIBERSAM*), and based on the experience of the Network of Research in Mental Disorders (Spanish acronym, REM-TAP),[4] the coordinated multicentre project entitled «Genotype-phenotype and environment interaction. Application of a predictive model in first-episode psychosis (PEPs Project)» was launched in January 2009.[5] This was at that time the study that had received the greatest financial support from the Healthcare Research Fund (Spanish acronym, *FIS;* PI08/0208) in the area of neurosciences. It also received intramural funding from CIBERSAM as a strategic consortium project. The PEPs Project focuses on identifying genetic and environmental factors of risk and their interaction in the appearance of a first-episode psychosis, so that more effective strategies of differential diagnosis, treatment and prevention of relapses can

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be developed. In this project, 16 consolidated biomedical research centres across Spain participated, with coordination from the Schizophrenia Unit at the Barcelona Clínic Teaching Hospital. A prospective longitudinal assessment with a 2-year follow-up was carried out using a sample of 335 individuals with first-episode psychosis, all between 7 and 35 years of age, whose signs and symptoms had not lasted longer than a year, plus 253 healthy individuals having the same socio-demographic profile. The study was built around a basic module in which all the groups participated and in which genetics and clinical situation were characterised (using standard clinical and socio-demographic scales) and 3 specific modules: neuroimaging, neurocognition and pharmacogenetic-therapeutic modules. This article presents a review of the main results and publications of the PEPs Project.

One of the possible diagnoses after a first-episode psychosis is schizophrenia. The genetic evidence in schizophrenia supports a multi-factor, polygenic and heterogeneous origin.[6] Research hypotheses based on genes that might be candidates for schizophrenia development have not been backed by complete genome association studies.[7–9] Genetic and environmental factors of risk need to be considered together, given that both are important in the aetiology of schizophrenia and they do not appear to work in isolation.[10] The most relevant results from the PEPs Project genetic studies provide very interesting clinical data, showing that the combination of risk factors (especially the environmental and genetic) make it possible to predict the risk of first-episode psychosis.[11] The predictive model developed shows good sensibility, appropriate specificity and precision. These findings highlight the importance of the neurotransmission of serotonin, which interacts with certain environmental stimuli and help the serotoninergic system to perform a key role in the regulatory stress network and in other systems involved in the appearance and development of psychotic disorders. Other general aspects obtained from the research in this general module have made it possible to identify specific genetic polymorphisms, such as Val158Met of the Catechol-O-MethylTransferase (COMT) gene; these polymorphisms seem to be more sensitive to the synergic effect of the environmental factors that have an early impact on neurological development, which leads to vulnerable phenotypes as a deficient early adjustment.[12] Another of the PEPs study publications focused on analysing the adjustment of a drug (risperidone) dose, finding that clinicians use a parallel intuitive dosing process for the CYP2D6 phenotype. These results justify the clinical use of CYP2D6 genotyping as we head towards personalised medicine.[13],[14] Negative symptoms received special attention in the PEPs Project, with analysis of the predictive factors of the course of signs and symptoms that showed a reduction in negative symptomatology a year after the presentation of first-episode schizophrenia; these results were maintained at 2 years.[15] Consequently, early presence of negative symptoms during the course of the condition, together with deficient premorbid adjustment, seems to be capable of predicting the more serious medium-term negative symptoms. Patients whose negative symptoms persisted showed worse evolution. We also found that, in samples of teenagers with early-onset disorders, persistent negative symptoms led to worse cognitive and [social] functioning.[16]

Cognitive impairment is so prevalent in patients with schizophrenia that it has been proposed as a diagnostic criterion for this condition; however, its elevated variability and lack of specificity limit its diagnostic usefulness.[17–21] It is considered to be a main characteristic of schizophrenia spectrum disorder and it is recognised as important because of, among other reasons, its impact on psychosocial functioning.[22],[23] In the PEPs Project, the neurocognition module characterised the patients by studying the interaction between clinical, socio-demographic and premorbid adjustment variables, and the association with cognition. A mild to moderate cognitive impairment compared to healthy controls was replicated, along with an association with poor premorbid adjustment; these, together with socio-demographic variables and greater antipsychotic drug doses, contribute to the development of cognitive deficits.[24],[25] Along the same line, Amoretti et al.[26] identified that a cognitive reserve points towards a reorientation of psychological interventions, aimed at cognitive rehabilitation in individuals with first-episode schizophrenia and at functional rehabilitation in those with first-episode affective psychosis. The neurocognitive and clinical differences between affective and non-affective PEP that existed in initial disorder phases diminished at 2 years. Worse executive function performance and the severity of the symptoms were factors predicting poor functional results for the patients with PEP.[27] Consequently, early intervention is fundamental, both in cases of PEP with predominant affective signs and symptoms and those that lack them.[28]

Many studies have indicated better cognitive performance in individuals with PEP that smoke compared to those who are non-smokers. However, the findings are controversial. The effect of tobacco use on cognitive function seems to be linked to better cognitive performance, but our results do not show this association.[29] The findings in neurobiological research on cannabis and cognition in psychosis differ. In the PEPs Project, the use of cannabis was shown to be linked to better performance in patients with a family history of psychosis, while it was related to worse performance in those without such a history.[30] These results, easy to misinterpret, are being discussed in light of the rest of the scientific literature, which indicates better premorbid functioning in those with a strong cannabis habit. It has been proposed that the interaction between the COMT Val158Met polymorphism and the BDNF Val66Met polymorphism with cannabis use increases the risk of psychosis, although the data are not conclusive. Early cannabis consumption and the presence of the met allele of the BDNF Val66Met polymorphism were significantly associated with the age of psychosis onset in the PEPs Project.[31]

Another aspect that is still subject to debate is the evaluation of the effect of antipsychotic drugs on the cognitive performance of patients in the first stages of psychosis. Because of this, the Navarra Hospital Complex group designed a study on the PEPs sample to investigate the impact of the dopaminergic and anticholinergic loads of the antipsychotics on the cognitive performance of patients with first-episode psychosis. Statistically significant associations were found between dopaminergic load and worse cognitive performance in the cognitive functions of processing speed, verbal memory and global cognition. Statistically significant associations were also seen between greater anticholiner-

gic load and worse performance in verb al memory.[32,33] These findings are of great clinical applicability to the extent to which optimising antipsychotic drug doses is recommended to achieve the lowest doses possible. Cognitive deficit evolution over time with the individual changes that patients experience with a first-episode psychosis has rarely been studied. A study on the individual trajectories of the cognitive performance in the PEPs sample at 2 years was performed.[34] This study demonstrated that most patients presented time-stable cognitive deficits. It was also shown that only 20% of the patients presented clinically significant, reliable changes (in 10%, their cognitive deficits became worse and, in the other 10%, they improved).

Global brain structure alterations in the patients with schizophrenia centre around reductions in brain volume and in connectivity, mainly in the areas that involve the superior and medial temporal cortex and the prefrontal cortex,[35,36] not attributable to medication.[37] Reductions in the grey matter density and white matter abnormalities are observed, as well as increased ventricular volume.[38] These abnormalities can progress from early in the condition; it has been suggested that they are more prominent in early-onset forms of the disorder. Brain anomalies are currently thought to exist before, during and after PEP onset.[39] The results of the PEPs Project emphasise that the structural brain differences vary non-linearly according to the age of onset; there are differences in the temporal and frontal areas in early-onset disorders compared to those that begin in adults (Pina et al., 2016). These results suggest more appropriate methodological strategies for studying individuals with PEP in moments other than those being used now. Turning to the loss of brain tissue and more severe signs and symptoms, these are associated with the neutrophil count in patients with PEP. This supports the hypothesis that the immune system is poorly regulated in the initial disorder stages and makes blood cell counts a promising indicator of schizophrenia severity; it could even lead to establishing new therapies.[40]

In the PEPs study, as a result of its observational and realistic design, the patients maintained their standard treatment. This has made it possible to obtain global information on the normal treatment and on the results in these patients in Spain.[41] General drug prescription for PEP treatment in Spain follows the recommendations of the clinical practice handbooks and allows reviewing the tests that back any future research on specific drug strategies to treat the early stages of psychosis, such as the role of clozapine, extended-release antipsychotics, antipsychotic combination and the use of benzodiazepines.[42] It has also been shown that patients in early stages of schizophrenia and other psychotic disorders are at extremely high risk of cardiovascular comorbidity and that their metabolic profile will become worse during the first 2 years.[43]

A project on the scale of the PEPs study has facilitated the creation of a specific subproject to test the inflammatory implications in this pathology: the «FLAMM-PEPs Project» (''Inflammatory alterations in schizophrenia: the search for biological markers in first-episode psychosis''). This was an associated study funded intramurally, carried out in 2010 and 2011 (P02). Part of the PEPs centres (6 clinical centres and 1 basic centre) participated in FLAMM-PEPs and it was coordinated by the Department of Pharmacology at the Faculty of Medicine of the Universidad Complutense in Madrid. It was a national, multicentre, prospective, longitudinal and observational study with a 1-year follow-up. The main objective was to identify possible biochemical pathways leading to an inflammatory and oxidative/nitrosative status in a subsample of approximately 100 patients with first-episode psychosis and 100 healthy individuals paired according to the PEPs Project criteria.

Reformulating the inflammatory theory and its involvement in severe mental disorders (principally in schizophrenia) led us to studying this in initial disorder stages.[44,45] The FLAMM-PEPs Project revealed a lack of regulation of the pro- and anti-inflammatory routes in mononuclear cells of peripheral blood [46], accentuated in later pathological stages.[47] Recent literature suggests that severe mental disorders are linked to inflammatory processes,[48] mainly in schizophrenia and related disorders.[44,49] A noteworthy finding from this study was that the anti-inflammatory mediator 15d-PGJ_2 could be used as a soluble plasma biomarker for PEP and might be a potential factor protecting against PEP, while COX-2 and NO-2 (the soluble and stable metabolites of nitric oxide) behaved as potential risk factors. Inflammatory status and cognitive function are linked in PEP. Cabrera et al.[50] report anti-inflammatory biomarkers of executive function and attention, which might be useful to monitor the course of cognitive impairment and would make it possible to identify a subgroup of patients based on these measurements; this would in turn facilitate orienting treatment programmes and provide instruments for choosing a personalised focus. FLAMM-PEPs has enabled establishing proposals for integrating global physical health care, especially early cardiovascular healthcare attention after PEP.[51] This project has also opened the way to complementary research strategies, such as those focused on the intestinal microbiota of patients with PEP and with other mental disorders.[52] The FLAMM-PEPs intramural study also made it possible to describe a peripheral dysregulation of the endocannabinoid system in patients with PEP.[53] The relationship between the expression of certain endocannabinoid system markers and cognitive function was later demonstrated.[54]

The objectives of characterising patients with first-episode psychosis were achieved and the elevated risk of relapse in the years after the remission of the PEP episode was confirmed. Consequently, a new 3-year longitudinal design on these patients was proposed. Using the same methods as with PEPs, a new study was developed: «2EPs Project» (''Clinical and neurobiological determinants of second schizophrenia episodes. Longitudinal study on first-episode psychosis''). Also funded by FIS (PI11/00325), this project began in 2011 and is currently finalising. In 2EPs, 15 of the 16 groups comprising the PEPs Project have participated, as well as a basic group, with the Schizophrenia Unit at the Barcelona Clínic Teaching Hospital likewise coordinating. Covering 233 patients with first-episode psychosis in the remission phase of no more than 5 years' evolution, its objective of 2EPs was to identify the factors related to relapses and their prevention. The protocol for the second episode research has a structure of 6 modules. The basic module assesses the presence or absence of relapses and includes the clinical evaluations, global functioning assess-

ment, genetic risk and the pharmacogenetics of efficacy and side effects. A second module (neuroimaging) encompasses analysing the brain structures involved in relapses using magnetic resonance imaging, while a third (neurocognition) determines cognitive profiles related to greater likelihood of having a relapse. A fourth module (adherence) aims at establishing antipsychotic drug levels in saliva as a method of monitoring drug compliance and assessing the potential benefits of psychoeducational and psychological treatment; a fifth module (biological) searches for markers involved in oxidative stress, inflammatory and anti-inflammatory phenomena, homocysteine, epigenetics and neurotrophins potentially involved in second episodes. The last module (physical health) focuses on patients with health complications and their risk of relapse. The analysis of these data promises to help to define early interventions centred on preventing second episodes of schizophrenia.

In summary, the PEPs Project has been an emblematic initiative that harvests the spirit of the CIBERSAM mission: promoting collaborative, translational biomedical research of excellence. The last few decades have witnessed an accumulation of knowledge thanks to advances in genetics, epidemiology and neuroimaging, as well as in pharmacology and neurocognition. This new information needs to be integrated for better understanding of psychopathology and to encourage strategy changes to discover new drugs and non-pharmacological interventions for mental health treatment.[2] We are helping to define a path leading towards precision psychiatry. This experience suggests that, using staging models, we could develop even primary and secondary strategies of prevention.[55] Prevention is possible and we need to cut the gap between scientific evidence and its application in standard clinical practice, especially in the area of psychoses as a paradigm of mental disorder.[56,57]

Funding

This study received economic support from the Spanish Ministry of Economic Affairs and Competitiveness (ref. ISCIII PI08/00208); the Carlos III Healthcare Institute, the European Regional Development Fund, the European Union, ''*Una manera de hacer Europa*/A Way of Shaping Europe''; the Centre for Biomedical Research in Mental Health Network (CIBERSAM), the CERCA Programme / the Catalan Government and the Catalan Secretariat of Universities and Research of the Department of Enterprise and Knowledge (2014SGR441 and 2014SGR398).

Conflict of interests

Dr. Miquel Bernardo has received research funding and has collaborated as a consultant or speaker for the following entities: AB-Biotics, Adamed, Angelini, Casen, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Takeda and Semantics; as well as from the Ministry of Education, Culture and Sport, the Ministry of the Economy, Industry and Competitiveness, the Ministry for Science and Innovation, the Carlos III Healthcare Institute, the Centre for Biomedical Research in Mental Health Network (CIBERSAM), the Catalan Government, the Secretariat of Universities and Research of the Department of Enterprise and Knowledge, the European Group for Research in Schizophrenia (EGRIS) Foundation and the Seventh Framework Programme of the European Union. Dr Jeronimo Saiz-Ruiz has participated as a speaker or an expert for Adamed, Lundbeck, Servier, Neurofarmagen, Otsuka, Indivior, Schwabe and Janssen; and has received research funding from public organisations (CIBERSAM, FIS, CAM and the University of Alcalá), the Canis Majoris Foundation, Lundbeck, Janssen, Medtronic and Ferrer. Dr Eduard Vieta has received research funding and has collaborated as a consultant or speaker for the following entities: AB-Biotics, Actavis, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute. The other authors have no conflicts of interest to declare.

Acknowledgements

We extend our thanks to all the participants. We would also like to thank the Carlos III Healthcare Institute, the Spanish Ministry of Science, Innovation and Universities, the European Regional Development Fund (ERDF/*FEDER*) (PI080208, PI11/00325 and PI14/00612) and CIBERSAM; and the Catalan Government, the Secretariat of Universities and Research of the Department of Enterprise and Knowledge (2017SGR1355).

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