Clinical utility of early intervention including the 5-Step Precision Medicine (5SPM) method in first-episode psychosis (the CLUMP project): Protocol for a cohort study with nested economic and process evaluations

Jesus Perez, David Heredero Jung, Oscar Gonzalo, Belen Garcia Berrocal, Carmen Garcia Cerdan, Pablo Salas Aranda, Alejandro de la Sota Perez, Sandra Lorenzo Hernandez, Elena Marcos Vadillo, Rocio Garcia Garcia, Vanesa Berdion Marcos, Ana Macia Casas, Belen Refoyo Matellan, Berta Bote Bonaechea, Llanyra García Ullán, Carolina Lorenzo Romo, Carmen Martin Gomez, Concha Turrion Gomez, Maria Isidoro Garcia

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Abstract

Background: Psychotic disorders, such as schizophrenia, present a significant challenge to healthcare systems due to their high disability rates and treatment costs. With discontinuation rates for antipsychotics reaching over 40% in the first year and 80% after three years, it is crucial to tailor antipsychotic selection and dosing early in treatment. Personalised precision psychiatry, underpinned by pharmacogenetics, holds considerable potential in individualising antipsychotic treatment for patients with first-episode psychosis. The internationally pioneering method called 5SPM (5-Step Precision Medicine) lets the application of pharmacogenetics to clinical practice. The recently launched PRevention and early INTervention in mental health (PRINT) programme in Salamanca, Spain, integrates this method to enhance early intervention for adolescents and young people with first-episode psychosis.

Objective: The CLinical Utility of early intervention including the 5-Step Precision Medicine (5SPM) Method in first-episode Psychosis (CLUMP) project aims to explore whether an early intervention model of personalised precision psychiatry, including pharmacogenetics, improves adherence to antipsychotic medicines and, therefore, clinical and functional outcomes in young people suffering from the first episode of a psychotic illness.

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Results: Ethics approval was obtained in June 2023. Recruitment for the CLUMP project began in January 2025, and enrollment for Cohort 1 will continue until May 2026. All data collection is expected to be completed by June 2027. Data analyses are estimated to take approximately six months. The project is scheduled to conclude on December, 2027.

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young people suffering from the first episode of a severe mental illness, such as schizophrenia. Clinical Trial: ClinicalTrials.gov NCT06453174; https://clinicaltrials.gov/study/NCT06453174

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Trial Registration: ClinicalTrials.gov NCT06453174; https://clinicaltrials.gov/study/NCT06453174

Keywords: First-episode psychosis; early intervention; precision medicine; personalised precision psychiatry; antipsychotics; schizophrenia.

Introduction

Psychotic illnesses, such as schizophrenia and related conditions, are a major issue for public healthcare systems; they cause enormous disability and are expensive to treat. As the illness becomes manifest during adolescence or young adulthood, non-specific signs, such as anxiety, depression, and emerging psychotic features, form a prelude to the full psychotic syndrome that may endure for months or even years before these people seek help or receive treatment. This duration of untreated psychosis (DUP) is inversely related to outcome. Therefore, providing effective treatments as soon as possible, shortening DUP, may prevent the development of a more severe illness, improve quality of life, and lead to recovery in many cases [1,2]. Many people at an early stage of their psychotic illness, in addition to delusions and/or hallucinations, may also develop cognitive problems that underpin disability. These impairments contribute to problems in functional outcome that are

regarded by patients and their relatives as important as the phenomena that professionals dwell focus on. Later, the evolution of psychotic disorders varies hugely and still raises the question of why certain people improve and other stay unwell despite having gone through similar interventions [1].

Specific psychological and pharmacological developments to tackle first presentations of psychotic illnesses have been relatively slow. However, services to deliver existing evidence-based interventions to people at that early clinical stage have changed dramatically over the last two decades. Traditional multidisciplinary community mental health teams now work as specialised early intervention in psychosis teams. Seminal work, especially from Australia and UK, led to widespread adoption of these assertive treatment programmes for young people in the initial phases of psychotic illnesses. In this context, rapid access and adherence to effective pharmacological treatments, specifically antipsychotics, play a fundamental part in “the shorter the DUP the better the outcome” motto early intervention in psychosis is predicated upon [1,2]. In fact, there is a plethora of evidence demonstrating that adherence to antipsychotic treatment has a positive impact on psychotic illness progression and longer-term outcomes, such as hospital admissions, functioning and suicide rates [3-5].

The introduction of early intervention programmes has led clinicians towards a more accurate identification of the psychological and social interventions each patient can benefit from; however, they still face difficulties in selecting the antipsychotic medicine that better suits them [6-8]. Thus far, pragmatic randomised controlled trials have been the main source of scientific information to decide on the most effective and tolerable antipsychotics for patients with first-episode psychosis. These studies have found all-cause discontinuation rates for individual antipsychotics of approximately 40% or above during the first year of follow-up, which increases to 80% after three years of treatment, even in the context of traditional early intervention in psychosis services [7,8]. These results fall short in shifting clinicians’ trial-and-error habit to prescribing antipsychotics in clinical practice, which often ends in switches from those that do not yield sufficient therapeutic response or cause adverse effects [4]. This is further complicated by the fact that patients’ early experiences of antipsychotics nurture long-term perceptions towards them; therefore, suffering side effects or a lack of efficacy can make young individuals develop negative attitudes towards these drugs [9]. In fact, the high prevalence of adverse reactions in young, drug-naïve patients and lack of therapeutic response from antipsychotics are significant contributors to treatment discontinuation [9,10]. This stresses the need to tailor antipsychotic (and dose) selection to each patient from the very early stages of their psychotic illness.

Whilst analytical and clinical validity of pharmacogenetics (the effect of genetic factors on reactions to medicines) in people treated with antipsychotics have already found strong associations between treatment responses, side effects and genetic variations, studies describing its clinical utility are very scarce and mainly limited to patients with severe and enduring psychotic disorders and poor response to treatment [11-13]. Notably, the systematic implementation of pharmacogenetics and its clinical effect on those suffering from the first episode of a psychotic illness has still not been tested. Personalised precision psychiatry using pharmacogenetics could help individualise antipsychotic treatment for patients with first-episode psychosis. It could reduce the time needed to find a tolerable and effective antipsychotic drug for people that were never exposed to such medications. Pharmacogenetics would simply be another tool that early intervention services could adopt and implement within their treatment pathways to improve medication adherence [13].

Our Unit of Pharmacogenetics and Precision Medicine at Salamanca University Hospital (HUS) in Spain has been working in the application of pharmacogenetics to clinical practice for more than a decade [14]. We have developed an internationally pioneering method called 5SPM (5-

Step Precision Medicine) that addresses most of the implementation challenges outlined above. The award-winning 5SPM is based on updated scientific knowledge, integrating new technologies, from up-to-date highly efficient genotyping to state-of-the-art bioinformatics and artificial intelligence [13-17]. In fact, 5SPM is paving the way for the implementation of pharmacogenetics across different clinical specialties. On the contrary to other existing methodologies, which are mostly guided by lab genetic results, the 5SPM also addresses the specific needs and characteristics of the patient is applied to, taking into consideration clinical and epidemiological variables as well as any other factor, such as polypharmacy, that could affect treatment response. The 5SPM model relies on a multidisciplinary approach, implying that technical and clinical staff must work closely together, and strictly adheres to ethical requirements, such as a comprehensive informed consent. This method has already shown quantifiable positive impact on the quality of life of patients in different clinical fields, including psychiatry. Since its inception, more than 1,000 patients have benefited from it and has also generated additional phamacogenetics knowledge [13,16,18]. The 5SPM methodology has already proved to be clinically useful and cost-beneficial in patients with diagnosable psychotic disorders and poor response to antipsychotic treatment [13,19].

We have fully integrated and shall evaluate the impact of the 5SPM method in our recently launched PRevention and early INTervention in mental health (PRINT) programme to treat adolescents and young people with first-episode psychosis in Salamanca. Considering there is still a marked heterogeneity in treatment engagement and response among patients with first-episode psychosis in early interventions services around the world [20], the PRINT programme will aim to refresh the early intervention model by optimising pharmacological choices for such clinical group following the 5SPM methodology.

Methods

The CLinical Utility of early intervention including the 5-Step Precision Medicine (5SPM) Method in first-episode Psychosis (CLUMP) project will test the hypothesis that an early intervention model of personalised precision psychiatry, including pharmacogenetics, will significantly improve adherence to antipsychotic medicines and, therefore, clinical and functional outcomes in young people suffering from the first episode of a psychotic illness.

Objectives

Our objectives will be to:

1. Introduce an innovative early intervention model of personalised precision psychiatry, including the 5SPM method, for patients with first-episode psychosis.
2. Ascertain whether such a model can reduce the elevated discontinuation rates of antipsychotic medications in this group within the first year of follow-up by clinical services.
3. Assess the impact of the new model on pragmatic efficacy measures, such as hospital admissions, and functional outcomes, such as return to work or education.
4. Determine whether this innovation can bring cost benefit to the public healthcare system and the wider economy.
5. Establish a blueprint for implementing this precision medicine model, specifically pharmacogenetics, across early intervention in psychosis programmes nationally and internationally.

Study design

To test our hypothesis and achieve our objectives, we shall compare adherence to the first prescribed antipsychotic medication and pragmatic clinical and functional outcomes between two cohorts of

patients with first-episode psychosis. One cohort will be comprised of patients treated before the implementation of an early intervention in psychosis model of personalised precision psychiatry including pharmacogenetics, and the other of patients treated under this new model. Also, we shall compare the pharmacogenetic profiles and possible phenocopies (variations of phenotypes produced environmentally, e.g., due to polypharmacy, rather than genetically) between these first-episode psychosis patients and a national sample of patients with longer-term psychotic disorders or with other mental health conditions, to evaluate potential implications for clinical management at different stages of a psychotic illness, and across mental disorders.

Participants

A total of 300 patients will be included in this project. We shall include different cohorts:

- Cohort one: A prospective sample of patients with a first episode psychosis referred over 18 months to the new early intervention in psychosis programme of personalised precision psychiatry (PRINT) at CAUSA.
- Cohort two: A retrospective, consecutive (in reverse chronological order as registered in CAUSA electronic health records) sample of patients who suffered a first-episode psychosis before the implementation of PRINT.

Inclusion and exclusion criteria for both cohorts will be aligned to the PRINT programme referrals acceptance criteria, which are predominantly inclusive:

- Inclusion criteria: Patients (1) with diagnosis of first-episode psychosis, either non-affective or affective; (2) aged 12-35; and (3) followed by clinical services for at least one year, or earlier if there was evidence of antipsychotic treatment discontinuation (See “Outcome measures”, below). Also, patients in cohort one, and/or their family or legal representatives, will have to provide written consent to take part in the CLUMP project, including pharmacogenetics analysis (See “Ethical considerations”, below). For patients in retrospective cohort two, this will not be an inclusion criterion, but all of them will be approached by our research team seeking their consent to obtain their pharmacogenetic profile for research purposes.
- Exclusion criteria: Patients (1) with first-episode psychosis due to organic causes, for example, brain diseases such as Huntington’s and Parkinson’s disease, human immunodeficiency virus, syphilis, dementia, brain tumours or cysts, or brain injury; (2) with moderate to severe intellectual disability; and (3) who spent (cohort two) or plan to reside (cohort one) most of the one-year follow-up period in a locality out of the PRINT’s catchment area.

For additional comparative purposes, we shall analyse environmental, clinical and pharmacogenetic information of patients with psychotic disorders of more than five years of evolution or with other mental disorders, whose data are currently stored, and ethically approved for research use, in our Unit of Pharmacogenetics and Precision Medicine at HUS.

Clinical management and pharmacogenetics analysis

Patients in cohort one will receive the recently introduced PRINT programme, an early intervention in psychosis model, including the 5-Step Precision Medicine (5SPM) method based on pharmacogenetics developed by our Unit of Pharmacogenetics and Precision Medicine at HUS. The 5SPM method includes five steps: (1) collection of clinical, epidemiological, and treatment data; (2) study of pharmacological interactions based on drug-specific pharmacokinetic pathways; (3) pharmacogenetic analysis of the genes that code enzymes involved in drug-specific metabolism; (4) introduction or change of pharmacotherapy according to the data obtained from the previous three

steps; and (5) analysis of the treatment outputs and reassessment if needed. These steps will be preceded by an informed consent process. This preliminary procedure plus steps 1-4 will be performed as soon as possible, ideally when the patient with a first-episode psychosis is identified by clinical services, aiming to minimise the time between the initial presentation and pharmacogenetics-informed decisions on pharmacotherapy. Step 5 (treatment review) will be carried out 6 months after antipsychotic treatment initiation. All steps will require a multidisciplinary approach, and a shared decision-making process including patients and/or their family/legal representatives, especially if the patient lacked mental capacity to make such decisions.

For the pharmacogenetics analysis (step 3), we shall employ mass spectrometry and real-time PCR to study the genes encoding enzymes 1A2, 2B6, 2C9, 2C19, 2D6, 3A4, 3A5 of the CYP450 cytochrome family, in addition to transporter ABCB1. The CYP450 superfamily contains highly polymorphic genes. The usual approach to the relationship between genotypic variability and the metabolism of CYP450 substrates is based on the definition of metabolic phenotypes with their characteristic pharmacokinetic implications according to different genetic mechanisms. Metabolic profiles will be considered to make decisions on antipsychotic treatment choices. We already have enough technical support and pharmacogenetics evidence for most antipsychotics employed in the early stages of a psychotic illness, i.e., olanzapine, risperidone, paliperidone, quetiapine, aripiprazole, amisulpride, lurasidone, cariprazine, haloperidol and zuclopenthixol.

Cohort two would have received the standard care provided by mental health services before the PRINT programme implementation.

Patient and public involvement

Patients have been involved in the design and will participate in the delivery of this trial. For instance, patients with first-episode psychosis were consulted on the feasibility of running this project and some of them were involved in its design, specifically on what information to include in the informed consent to carry out the pharmacogenetics analyses. In addition, we shall constitute the CLUMP Patient and Carer Advisory Group, who will also contribute to the identification of themes for the qualitative evaluation (See section “qualitative evaluation,” below).

Outcome measures

Primary outcome measure

The primary outcome to measure treatment adherence will be all-cause discontinuation, following the patient´s and/or treating clinician´s decision, of the initially assigned antipsychotic medication. All-cause discontinuation rates in the CLUMP project will be defined by all-cause discontinuation proportions during one-year follow-up, and the mean time to such discontinuation.

For cohort one, the one-year follow-up period will start when antipsychotic medication is prescribed taking into consideration the pharmacogenetics advice emerging from the 5SPM method. For cohort two, follow-up would begin the date when the first antipsychotic medication was prescribed. For both cohorts, the first assigned antipsychotic will be the initially prescribed antipsychotic drug for maintenance treatment, not only for a short-term use to control psychomotor agitation. Also, in accordance with existing scientific consensus, the discontinuation date will be defined as the first day of a 2-week or longer interruption of the first prescribed antipsychotic. In cohort two, treatment discontinuation dates will be determined by examining clinical records. Where only approximate dates were available, the first, middle or final day of the month will be used as best estimates. When cross-titration of medication took place, the date of discontinuation will be the first day of the cross-tapering process.

All-cause discontinuation will also be stratified by four reasons: (1) Insufficient efficacy, (2) adverse events, (3) lack of adherence, and (4) other. Insufficient efficacy will be established at the treating clinician's judgment only after at least 3 weeks of treatment. If more than one reason for discontinuation was present, we shall select one by applying the ranking order as stated above.

Secondary outcome measures

We shall also collect pragmatic efficacy, tolerability, and functional outcome measures in both cohorts. These will include evaluations during the follow-up period of hospital admissions, visits to accident and emergency departments and outpatient clinics, changes and number of medications, changes in antipsychotic dose over time, using chlorpromazine dose equivalents as reference, type and number of side effects, including impact on body mass index, and initiation or return to work or academic activities.

As part of routine practice, patients in cohort one will also be assessed with the quality-of-life self-complete questionnaire EQ-5D-5L to determine overall improvement over time. Scores from this questionnaire will also feed into the 5SPM step 5 to make treatment decisions at month 6. This cohort will also be evaluated with a battery of questionnaires including the Positive and Negative Symptoms Scale (PANSS) [21], Calgary Depression Rating Scale [22], Brief Negative Symptoms Scale (BNSS) [23], and the UKU side effects rating scale [24].

Effect and sample size

We performed a power calculation for the main outcome: the proportion of patients with first-episode psychosis who, by their treating clinician and/or their own decision, discontinue, for any reason, the first assigned antipsychotic medication within one-year. As stated before, recent research studies, mostly carried out in early intervention settings, concur that 40% of the patients with first episode psychosis experience first-prescribed antipsychotic drug discontinuation during the first year following treatment initiation [7,8]. This proportion may be even higher in patients receiving mainstream psychiatric care, such as our cohort two. Considering the expectations behind the use of personalised precision medicine, PRINT should aim to reduce discontinuation rates to 10%. Therefore, for power of 80% with (1) a significance level of 0.05 (two-sided), (2) all-cause discontinuation rate in cohort one (treatment-as-usual) of 0.4, (3) all-cause discontinuation rate in cohort two (intervention) of 0.1 and (4) an expected drop-out/loss to follow up rate of 0.2, our calculations would require a sample size of at least 38 patients in each cohort. We employed the R Statistical Software pwr package for this calculation (version 4.4.2 for Windows, The R Foundation).

In CAUSA, we have found an administrative incidence of 50 new patients aged 12-35 every year. Thus, we would expect at least 75 patients eligible to be recruited for cohort one over 18 months. Using a conservative approach, if 25 (approx. 35%) did not agree to take part, we would still enrol 50 patients. This would be in addition to another 50 patients in our retrospective cohort two, and pharmacogenetic data currently available at CAUSA from 100 patients with psychotic disorders of more than five years of evolution and another 100 with other mental disorders that we shall employ for further comparative purposes, as outlined before. This all accounts for a total of 300 participants contributing to this project.

Statistical analysis

Comparisons of the main outcome, i.e., discontinuation rates, will be carried out performing chi-squared test. Kaplan-Meier survival curves and multivariate log-rank tests will be used to assess time to all-cause antipsychotic discontinuation. For these analyses, patients will be followed up for a year, from antipsychotic treatment initiation until discontinuation. Thus, we shall censor survival time by

the end of the one-year observation period or before such date if there was enough evidence of antipsychotic discontinuation. We shall describe and compare sociodemographic information, and clinical and functional outcomes within and between groups. Means and standard deviations will be used to describe quantitative variables. We shall employ chi-squared test or Fisher´s exact test for categorical variables and Mann-Whitney U test for continuous variables, among others. Data analyses will be performed with R statistical software (version 4.4.2 for Windows, The R Foundation).

Qualitative evaluation

We shall aim to interview 15 patients from cohort one to know their views on the PRINT programme, specifically on the implementation of the 5SPM method. We shall recruit participants who complete the one-year follow, but also some who might withdraw treatment before then. In principle, the interviews would explore the following thematic questions:

1. How far the goals of personalised precision psychiatry based on pharmacogenetics were aligned with the patients' own goals?
2. Did it help in achieving their goals, what did not, and why?
3. Is there anything that could have been performed differently during the informed-consent and 5SPM processes?
4. What might have contributed to non-engagement and treatment discontinuation?
5. What would help them meet their goals and priorities better, and why?

As stated in the section "patient and public involvement," the CLUMP Patient and Carer Advisory Group will also contribute to the identification of additional themes for the qualitative evaluation.

We shall use purposive, quota sampling to ensure diversity, especially with regards to gender. The CLUMP project team will also be interviewed to characterise their experiences implementing the new model. An independent researcher will conduct all the interviews that will be audio-recorded and transcribed verbatim. Data analysis will be based on the constant comparative method. This will involve intensive engagement with the data, using comparison across datasets to generate higher-order themes with explanatory value. NVIVO software will be used to assist in coding the data.

Economic evaluation

We shall explore cost-benefit using the primary outcome measure: all-cause discontinuation. The time-horizon will be one-year post antipsychotic initiation for both cohorts. Costs and outcomes will be compared at the final follow-up point and presented as mean values by cohort with standard deviations. The costs will be estimated using service use data. We shall collect these data using an adapted Spanish version of the Early Intervention Adult Service Use Schedule (AD-SUS) [25], which contains costs that are easy to track and calculate in the Spanish health system. The Early Intervention AD-SUS will be completed for both cohorts. The measure covers use of all health and social care services over 12 months (with an interim collection at 6 months), as well as socio-demographic information and employment status. In cohort one, we shall also perform a cost-utility analysis using Quality Adjusted Life Years (QALYs) derived from the EQ-5D-5L.

Data management

Data collected for the CLUMP project will be narrative and numeric, and will be obtained from interviews, review of clinical record and blood tests. They will include sociodemographic information, pragmatic outcome measures, questionnaires to measure efficacy, functioning and tolerability, and pharmacogenetic information.

As with all clinical data, the findings from this study will be kept confidential to protect personally identifiable information. To ensure that all information collected about participants remains confidential, we will only use anonymised participant information. Codes linking the identity of the participant to clinical data will be held on a secure password-protected database. Personal data needed to contact the subject will be securely stored on a separate secure database. Only the project team and professionals working at the clinical services the individuals are recruited from or at the Unit of Precision Medicine and Pharmacogenetics in HUS will have access to the participant's personal data. Only non-identifiable participant data will be transferred to a central database for the project, and only non-identifiable information will be made available to any other researchers or collaborators involved in the study. All data will be encrypted and stored in secure databases on a secure network, using established procedures. All study personnel will have to be certified to conduct research with human subjects and will be aware of the importance of maintaining strict confidentiality. Clinical notes will not be accessed by those outside the direct health care team, which includes members of the research team, until consent from participants is in place. Any hard copies of all data and records, including consent forms, will be stored in locked filing cabinets in locked rooms in security-protected buildings. Electronic and hard copies containing data from the project will be stored at CAUSA buildings and electronic facilities for a minimum of 10 years in accordance with good research practice. The storage of blood samples leftovers will be addressed in accordance to the informed consent signed by the patient and current legislation.

The final responsibility over the use of personal data will rest with the Specialised Clinical Assistance Managerial Office at CAUSA, and the Data Protection Officer at the Regional Ministry of Health will be contactable by all personnel involved and research participants. All data processing will be subject to the Spanish Organic Law 3/2018 for personal data and digital rights protection, and the European Union General Data Protection Regulation (GDPR) 2016/679 . GDPR articles 6, on lawfulness of data processing, and 9, on processing of special categories of personal data, such as genetic information, will be particularly relevant for this project. Also, participants will have the rights to have access to and rectify their data or, eventually, limit or oppose to their use under the terms included in articles 15 to 23. They can execute these rights before the Principal Investigator for this project, and the Data Protection Officer. Participants will be informed that they can also present complaints with regards to the use of their data to the Spanish Agency of Data Protection.

Ethical considerations

Approval for this project was obtained from the Ethics Committee of the Salamanca Health Area for Research with Medicines (ref. PI 2023 06 1308). This study is registered at ClinicalTrials.gov (NCT06453174).

Results

Recruitment for the CLUMP project began in January 2025, and enrollment for Cohort 1 will continue until May 2026. All data collection is expected to be completed by June 2027. Data analyses are estimated to take approximately six months. The project is scheduled to conclude on December, 2027.

Discussion

The CLUMP project aims to improve adherence and outcomes of patients with first-episode psychosis through the implementation and evaluation of an innovative early intervention programme of personalised precision psychiatry based on pharmacogenetics.

To date, the uptake of pharmacogenetics testing in psychiatry is limited to very few contributions and mainly focused on affective disorders, such as depression [6,11]. This is at odds with strategies around the world, planning to implement precision medicine as part of policies to enhance the uptake of genomic-driven medicine, including psychiatry. For instance, the UK National Health Service (NHS) has set up a Genomic Medicine Service with the aim of making pharmacogenetics part of routine clinical practice. Recently, the Royal Dutch Association of the Advancement of Pharmacy Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetic Implementation Consortium (CPIC), have developed evidence-based pharmacogenetics prescribing guidelines, which are compiled in the Pharmacogenomics Knowledge Base (PharmGKB) and rated by gene-drug pairing level of evidence [6,11,26,27]. These guidelines include antipsychotics and recommend that clinicians should consider genotyping of patients who experience inefficacy or side effects with any of the drugs that have enough pharmacogenetic evidence. This information could then be used to personalise prescribing decisions. Pharmacogenetics in psychiatry has mainly focused so far on pharmacokinetics and there is consensus that genetic information related to enzymes of the cytochrome P450 (CYP) family, such as CYP2D6 and CYP2C19, can be employed to provide treatment advice. In fact, it is estimated that between 36 and 62% of the population have variants of these two isoenzymes that may modify the metabolism of psychiatric medications [6,28]. However, although current pharmacogenetics guidelines are used by an increasing number of mental health professionals, they do not take polypharmacy into consideration and their full integration in mental health care is still a worldwide challenge [6].

Even though patients and clinicians perceive the value of pharmacogenetics in mental health and the potential positive impact on patients' engagement and trust on both the prescribed medication and the prescriber, certain barriers preclude its successful implementation. For instance, mental health professionals feel they lack pharmacogenetics theoretical and practical knowledge, i.e., how to make use of it as part of their practice; and have concerns about how to integrate it within their workloads without increasing consultation times or delaying treatment decisions for too long. They worry about this genetic information replacing clinical judgement, or the risk of misinterpretations, mixing up strength of drug-gene interactions with overall drug effectiveness and not paying enough attention to other important environmental and biological factors that play a role in treatment response. Also, this innovation is not free of ethical considerations, such as the potential psychological consequences of disclosing pharmacogenetics results to patients or matters related to genetic privacy. Furthermore, research studies have rarely measured clinical effects or cost-benefit associated with pharmacogenetics application and existing guidelines mostly advice on the pharmacogenetics of individual drugs, without considering the common use of polypharmacy in clinical practice [6,11]. This all reflects, to a large extent, the lack of clear methodologies to embed and measure the impact of pharmacogenetics in day-to-day psychiatric practice.

Therefore, the problem that we strive to solve is cultural, linked to prevailing trial-and-error prescribing of antipsychotics in clinical practice, as well as structural, concerning the evidence-policy-practice gap for tailoring drug treatments to patient with psychotic disorders at the earliest opportunity. Nonetheless, our new joint venture of early intervention in psychosis and applied precision medicine, added to our previous experience using 5SPM for patients with mental disorders, should give us the scientific and logistic traction to achieve our aims. Indeed, a guided implementation of pharmacogenetics for real-world clinical settings, following the 5SPM methodology, could help overcome patients´ and clinicians' uncertainties and facilitate the use of this evidence-based innovation, not only to address poor response or adverse events from psychiatric medications in patients with established psychotic disorders, but also to promote personalised and pre-emptive drug prescription [11]. The CLUMP project should be able to provide the first clear

blueprint for implementing and evaluating the impact of personalised precision psychiatry based on pharmacogenetics in the context of early intervention programmes for the benefit of young people suffering from the first episode of a severe mental illness, such as schizophrenia.

Limitations

Since we will carry out the CLUMP project in one centre this might affect the generalisability of our results. Nevertheless, Salamanca has a university that attracts every year more than 40,000 students within our participants´ age range, and a province with diverse young population, some of them living in socially deprived areas. These characteristics will temper this limitation. On the other hand, given our project´s originality, we considered important to test our hypothesis in a relative circumscribed location and, later, move towards its implementation at scale. Also, our prospective cohort one may be affected by a status quo bias, i.e., attempts to maintain the pharmacogenetically-guided prescription despite lack of efficacy or presence of adverse events. This will be controlled with other pragmatic outcome measures, and the 5SPM step 5 at month 6, which will include questionnaires, such as EQ-5D-5L, to inform treatment maintenance or change.

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Authors’ contributions

JP, MIG, CTG, DHJ, BGB, CLR and CMG were involved in conceptualisation and funding acquisition for this project. MIG, JP, OG, CGC, PSA and ASP participated in the development of materials for data collection. MIG, DHR, BGB, SLH and EMV designed and decided on lab methodologies and technical support. JP, CGC, PSA, RGG, VBM, AMC, BRM, BBB, LGU, CLR, CMG elaborated the strategy for clinical evaluations and will support all clinical aspects of this study. JP and MIG wrote the first draft of the manuscript. OG reviewed and completed such draft. All authors reviewed and contributed to the final version of the manuscript. JP and MIG are will supervise this project.

Conflicts of Interest

None declared.

Abbreviations

5SPM: 5-Step precision medicine method
CAUSA: Salamanca University Healthcare Complex
CLUMP: CLinical Utility of early intervention including the 5-Step Precision Medicine Method in first-episode Psychosis project.
HUS: Salamanca University Hospital
DUP: Duration of untreated psychosis
GDPR: European Union General Data Protection Regulation 2016/679
PRINT: PRevention and early INTervention in mental health programme

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Supplementary Files

Multimedia Appendixes

Peer review docs.
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