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Pharmacogenomics is the future of prescribing in psychiatry

By Adam Jameson, Beth Fylan, Greg Bristow, Alastair Cardno, Caroline Dalton, Gurdeep Sagoo, Jaspreet Sohal & Samantha McLean

One in four people will experience a mental health condition during their lifetime (1), and medicines are commonly prescribed to help people during these difficult experiences. COVID-19 has exacerbated this, with annual antidepressant spending in the NHS increasing by £140m since the start of the pandemic (2). Antipsychotic prescribing has steadily increased over the past decade too (3).

Those working in mental health pharmacy regularly see the challenges relating to these medications.

A major challenge in psychiatry is non-adherence. Adherence to mental health medicines could be as low as 40–50% (4), despite it being an important factor in improving patient outcomes. Alongside patient preference and clinical parameters, a trial-and-error approach to prescribing psychiatry medicines is often used, which can mean frequent medication switches from those that do not yield the required therapeutic response or lead to adverse drug reactions (ADRs). The high prevalence of ADRs and lack of therapeutic response from psychiatric medicines are both factors driving poor adherence (5, 6).

In recent decades, the role of genetics in contributing to inter-individual variability in drug response has been established (7). Pharmacogenomics is the study of how variation in a person's genetic sequence can influence their response to medicines. This can be both pharmacodynamically — how the drug exerts its therapeutic action — and pharmacokinetically — how the drug moves through the body (8). Pharmacogenetic testing can be used to identify genetic variants responsible for this altered response, by obtaining a patient sample (e.g., blood or saliva) and genotyping this in the laboratory. Pharmacogenomic-guided prescribing can then improve the precision of prescribing, reducing the reliance on trial-and-error prescribing approaches by using a more tailored method.

In March 2022, the Royal College of Physicians and the British Pharmacological Society published the 'Personalised prescribing' report (9). This outlines the potential opportunities for pharmacogenomic-guided prescribing and how barriers to its uptake, such as funding, service design, education and training, clinical decision support and patient engagement can be addressed. Using pharmacogenomics to reduce ADRs from antipsychotics and antidepressants is highlighted as an opportunity in the report.

This coincides with the production of the first clinical guidelines for the use of pharmacogenetic testing in psychiatry, authorised by the Dutch Psychiatric Association (NVvP) (10). These guidelines recommend that clinicians should consider genotyping if patients experience inefficacy or side effects with antidepressants and antipsychotics that have pharmacogenetic recommendations, especially if trialled medicines have similar cytochrome P450 (CYP450) metabolism routes. This can help determine if metaboliser status has contributed to inefficacy or side effects, and this pharmacogenetic information can then be used to personalise future prescribing decisions.

The NHS Genomic Medicine Service (GMS) is embedding genomic medicine at scale into NHS care, including pharmacogenomics and precision medicine (11). NHS England has convened an expert test evaluation working group for pharmacogenomics (12), which will use an ethical evidence-based approach to review drug-gene associations and provide advice to support the development of the NHS England test directory (13). As evidence for

pharmacogenomics in psychiatry develops, NHS England will continue to consider the cost-benefit balance of expanding the national genomic test directory to include pharmacogenomic tests for psychiatry.

Could pharmacogenomics help improve antipsychotic prescribing?

As part of a PhD project at the University of Bradford, sponsored by the Bradford District Care NHS Foundation Trust (BDCT), we have summarised the barriers and enablers (see Table) to implementing pharmacogenetic testing in mental health settings (14). Throughout the remainder of the project, using qualitative and quantitative methods, we will further explore issues relating to the implementation of pharmacogenetic testing in mental health settings. The project will focus specifically on how pharmacogenomics can be used to support antipsychotic prescribing in first episode psychosis (FEP). It is hoped we can gather perspectives towards using pharmacogenomics in FEP and demonstrate how its use can reduce the reliance on trial-and-error antipsychotic prescribing approaches.

Barriers:	Enablers:
<ul style="list-style-type: none"> • Cost or funding • Lack of knowledge about pharmacogenomics • Issues integrating pharmacogenomics into current workflows • Risk of misinterpreting results from pharmacogenomics tests • Fear of discrimination owing to pharmacogenomics test results • Fear that pharmacogenomic results could replace clinical judgement • A lack of clear guidance on the use of pharmacogenomics in psychiatry 	<ul style="list-style-type: none"> • General interest in pharmacogenomics • Belief that pharmacogenomics will lead to precision medicine • Perception that pharmacogenomics can aid the clinician-patient relationship • Belief that pharmacogenomics will become a standard part of care • Perception that pharmacogenomics can reduce adverse drug reactions • Belief that pharmacogenomics can be useful for patients with treatment failure • Low risk of psychological distress in patients receiving pharmacogenomic results

Table: Summary of the barriers and enablers to pharmacogenetic testing implementation in mental health settings (14)

Many working in mental health will understand the difficulty that healthcare professionals face when trying to communicate the importance of antipsychotic adherence. Clinicians appreciate the benefit that antipsychotics can provide in terms of quality of life and social functioning, but also understand why individuals have reservations about taking antipsychotics, as explained above. As a research team this is where we believe pharmacogenomics can help.

Why focus on first episode psychosis?

Antipsychotics play a critical role in symptom management both during and following FEP. But antipsychotic-naïve individuals have a higher risk of ADRs (15): a major contributor to antipsychotic discontinuation (16). Yet, adherence can positively impact on illness progression and longer-term outcomes, such as relapse, hospitalisation, and suicide rates in those who experience psychosis (17-20).

Initial experiences of antipsychotics have been found to contribute to long-term attitudes towards antipsychotics (21). This means that experiencing ADRs or a lack of efficacy can cause individuals to develop negative perceptions towards antipsychotics, impacting on their willingness to adhere to them in the future (22).

By using a pharmacogenomic approach to antipsychotic prescribing, adherence may improve by reducing the prevalence of ADRs and increasing the likelihood of therapeutic response. With this, the benefits of antipsychotic adherence can be realised and longer-term attitudes towards antipsychotics will likely improve. The time it takes to find the most appropriate antipsychotic for an individual may also be reduced. By tailoring antipsychotic selection and dose to individuals, we hope these difficult conversations around antipsychotic adherence could be made a little easier.

The project so far...

A cross-sectional analysis of antipsychotic prescribing in the BDCT Early Intervention in Psychosis (EIP) service found that three in every four antipsychotics prescribed had a pharmacogenetic association, according to the PharmGKB database on drug-gene pairs.

This represents an urgent clinical need for NHS mental health settings, in particular EIP services, to follow other clinical specialties in the NHS by integrating pharmacogenetic testing services into treatment pathways. This will allow prescribing of antipsychotics, including aripiprazole, risperidone, olanzapine, quetiapine, haloperidol, clozapine, and zuclopenthixol (23-25), with pharmacogenetic associations to be tailored to individuals, based on their genetic profile. This may include altering the dose of an antipsychotic or avoiding specific antipsychotics owing to the risk of inefficacy or ADRs.

In the future we believe that pharmacogenomics will be a routine clinical factor that is assessed when making prescribing decisions. Just as prescribers consider renal, hepatic or cardiac function, blood results, allergies, sex, age or ethnicity, pharmacogenetic data can also be embedded into patient records and clinical support systems, and used as an additional piece of clinical information to support prescribers in practising evidence-based medicine.

This could help to address the day-to-day challenges patients and healthcare professionals face in mental health settings across the NHS. Pharmacogenomics could also reduce costs to the NHS, by preventing hospitalisations owing to ADRs and decreasing the time taken trying to find a tolerable and efficacious antipsychotic when using a trial-and-error approach.

By improving medicines optimisation for our mental health populations, pharmacogenomics can increase the safety and effectiveness of psychiatric medicines.

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