The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Utilizing pharmacogenetics when treating first episode psychosis

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The parents of a 21-year-old man brought him to an emergency psychiatric clinic for disturbed behaviour. He displayed significant hallucinatory behaviour, prominent delusions of persecution involving "special forces" and notable disorganization of speech, and had experienced more than 8 months of socio-occupational dysfunction. Upon admission, neurologic examination was unremarkable and results of routine metabolic, endocrine, liver and renal screening were within normal limits. He met the diagnostic criteria for schizophrenia, with a first episode of untreated psychosis.

He was prescribed 10 mg aripiprazole for 4 days, but quickly developed adverse effects with disabling extrapyramidal rigidity. He then was switched to 2 mg risperidone, but after 1 week, he presented hypersalivation and debilitating daytime sleepiness. Despite ongoing hallucinations and persecutory fears, he refused the options of clozapine, olanzapine and quetiapine owing to concerns about weight gain, but he accepted haloperidol. He was put on 5 mg haloperidol, but he soon reported tremors, stiffness and a notable anhedonia.

At this stage, we sought a cytochrome P450 (*CYP450*) genotype assay for *2C19* and *2D6*. The patient was found to be a normal (extensive) metaboliser for *2C19* but a poor metaboliser (PM) for *CYP2D6*.

Haloperidol, aripiprazole and risperidone are likely to be degraded too slowly in patients who are *CYP2D6* PM, leading to treatment failure, and risperidone is likely to be too slowly converted to its active metabolite, leading to a greater risk of adverse effects. The patient consented to be switched to paliperidone, and a rapid antipsychotic response followed over the next 10 days. The patient was discharged on 6 mg/d paliperidone and had a score of 2 on the Clinical Global Impressions Scale of Severity at 6 months.

Most antipsychotics are hepatically metabolized by several CYP450 enzymes, but some, like paliperidone or amisulpride, are less metabolized than others.[1] In clinical practice, pharmacogenomic testing of *CYP2D6* and *CYP2C19* is seldom done, likely because many prescribers do not consider genetic factors to be critical for treatment choice, dose titration or adverse effect reduction.[2] The prevalence of PMs and ultra-rapid metabolizers (UM) is estimated to be less than 5% in Europeans (with notable variations across other ethnicities[4,5]); preventive testing is deemed to have low yield in practice. Thus, the maximum daily doses recommended for antipsychotics are based on a genotype-weighted population equilibrium that ignores the clinical relevance of *CYP2C19*/*CYP2D6* metabolizer categories. Nevertheless, several product labels offer dosing recommendations based on metabolizer status,[2] and many commercial tests are now available to assist prescribers.[5]

Of relevance to the present case is a recent large retrospective observational study confirming the higher frequency of treatment failures in PMs.[6] *CYP2D6* PMs are 2–3 times more frequent than UMs among Europeans,[3] with a notable dose reduction for aripiprazole and risperidone often reported in PMs.[6,7]

In patients with a first episode of psychosis, where a good response to pharmacotherapy is expected in most cases, the presence of repeated treatment failures and/or higher sensitivity to adverse effects should incite clinicians to order pharmacogenetic testing. This is particularly true if there are no other factors that explain poor response (e.g., noncompliance, drug abuse) or high sensitivity to adverse effects (e.g., medications interfering with the CYP system, a phenomenon known as "phenoconversion").[8]

In clinical practice, pharmacogenetic variations may not explain all of the variance in drug metabolism, and it is important that we consider sex,[9] age, concomitant medications, renal/hepatic status, lifestyle factors such as smoking, and weight when making antipsychotic prescribing decisions. Further, dosing and monitoring drug concentration may be more readily available and directly inform dose adjustments, complementing pharmacogenetic testing. Nevertheless, studies of real-world utility of pharmacogenetic testing indicate that certain subgroups, such as the most severely ill[10] or those who are nonadherent to treatment,[11] may have substantially greater odds of improvement when prescribing follows pharmacogenetics-based recommendations. Regarding antipsychotics, prescribing guidelines have been developed only for CYP2D6[2] and CYP3A4,[12] and the evidence for testing other variants[13] has not yet been deemed sufficient to make more general recommendations.

Increasing prescribers' use of pharmacogenetic testing in psychosis programs, especially when facing inadequate treatment response, has the potential to improve remission rates and reduce overall adverse effects associated with antipsychotics in clinical practice.

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Competing interests: R. Joober served as speaker and member of advisory board committees for Pfizer, Janssen, BMS, Sunovian, Myelin, Otsuka, Lundbeck, shire and Perdue. He also received grants from Janssen, BMS, Otsuka, Lundbeck, Astra Zeneca and HLS. P. Sabesan has received speaker fees from Lundbeck Canada. L. Palaniyappan is co-editor in chief of the *Journal of Psychiatry and Neuroscience* but was not involved in the review of or decision to accept the manuscript for publication. He has received personal fees from Janssen Canada, Otsuka Canada, SPMM Course Limited UK, and the Canadian Psychiatric Association; book royalties from Oxford University Press; and investigator-initiated educational grants from Sunovion, Janssen Canada, and Otsuka Canada. All of these are unrelated to the present work. No other competing interests were declared.

Funding: L. Palaniyappan receives research support from the Monique H. Bourgeois Chair in Developmental Disorders and Graham Boeckh Foundation (Douglas Research Centre, McGill University) and acknowledges a salary award from the Fonds de recherche du Quebec-Sante (FRQS).

Cite as: *J Psychiatry Neurosci* 2023 January 3;48(1). doi: 10.1503/jpn.220154

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