**Toward personalized medicine in schizophrenia: Genetics and epigenetics of antipsychotic treatment**

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**Abstract**

[Schizophrenia](https://www.sciencedirect.com/topics/neuroscience/dementia-praecox) is a complex [psychiatric disorder](https://www.sciencedirect.com/topics/neuroscience/psychopathology) where genetic, [epigenetic](https://www.sciencedirect.com/topics/medicine-and-dentistry/epigenomics), and environmental factors play a role in disease onset, course of illness, and treatment outcome. Pharmaco(*epi*)genetic research presents an important opportunity to improve patient care through prediction of medication side effects and response. In this narrative review, we discuss the current state of research and important progress of both genetic and [epigenetic](https://www.sciencedirect.com/topics/medicine-and-dentistry/epigenomics) factors involved in [antipsychotic](https://www.sciencedirect.com/topics/medicine-and-dentistry/typical-antipsychotic) response, over the past five years. The review is largely focused on the following frequently prescribed antipsychotics: [olanzapine](https://www.sciencedirect.com/topics/medicine-and-dentistry/olanzapine), [risperidone](https://www.sciencedirect.com/topics/medicine-and-dentistry/risperidone), [aripiprazole](https://www.sciencedirect.com/topics/medicine-and-dentistry/aripiprazole), and [clozapine](https://www.sciencedirect.com/topics/medicine-and-dentistry/clozapine). Several consistent [pharmacogenetic](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacogenetics) findings have emerged, in particular [pharmacokinetic](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacokinetics) genes (primarily [cytochrome P450](https://www.sciencedirect.com/topics/medicine-and-dentistry/cytochrome-p450) enzymes) and [pharmacodynamic](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacodynamics) genes involving dopamine, serotonin, and [glutamate](https://www.sciencedirect.com/topics/medicine-and-dentistry/glutamic-acid) [neurotransmission](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurotransmission). In addition to studies analysing [DNA sequence](https://www.sciencedirect.com/topics/medicine-and-dentistry/dna-sequence) variants, there are also several pharmaco*epigenetic* studies of [antipsychotic](https://www.sciencedirect.com/topics/medicine-and-dentistry/typical-antipsychotic) response that have focused on the measurement of [DNA methylation](https://www.sciencedirect.com/topics/neuroscience/dna-methylation). Although pharmacoepigenetics is still in its infancy, consideration of both genetic and epigenetic factors contributing to antipsychotic response and side effects no doubt will be increasingly important in personalized medicine. We provide recommendations for next steps in research and clinical evaluation.

**Introduction**

The contribution of genetic risk factors to schizophrenia (SCZ) has been supported by the high heritability of 79–85% and a concordance rate in monozygotic twins estimated at 41–65% (Cardno and Gottesman, 2000; Hilker et al., 2017; Wray and Gottesman, 2012). A substantial body of evidence supports that SCZ is a complex disorder of multifactorial origin with a range of symptoms that can be attributed to both genetic and environmental factors (Sawa and Snyder, 2002). Furthermore, twin studies have provided strong evidence for gene-gene and gene-environment interactions in the etiology of SCZ (Sullivan, 2005). However, the likely polygenic nature of SCZ is thus far showing only small effect sizes for individual genes, making etiologic understanding challenging.

Epigenetics bridges the gap between the genome and the environment and may explain the high heritability but low concordance rate between monozygotic twins (Dempster et al., 2011; Labrie et al., 2012; Viana et al., 2017). Epigenetics refers to dynamic, chemical modifications made to the structure of DNA that regulate gene expression but do not alter the DNA sequence (Petronis, 2010). DNA methylation is the most widely studied type of epigenetic modification in general and has been investigated as a risk factor for SCZ (Montano et al., 2016). Addition of methylation to genes in the dopaminergic (Melas et al., 2012; Nour El Huda et al., 2018), serotonergic (Ghadirivasfi et al., 2011), and brain-derived neurotrophic factor pathways (Ikegame et al., 2013) have been reported to be significantly associated with SCZ. Furthermore, epigenome-wide studies have also generated encouraging results. For instance, Jaffe et al. (2016) have reported significant differences between SCZ patients and controls with enrichment for genes involved in neurodifferentiation and development. More recently, a meta-analysis of epigenome-wide studies found significant methylation differences associated with psychosis, SCZ, and treatment-resistant SCZ (Hannon et al., 2021).

The introduction of antipsychotics in the 1950s revolutionized our understanding and approach to SCZ treatment and has markedly improved the quality of life for SCZ patients. However, there exists a large variability in treatment response and tolerability to these medications among individuals, making discovery of treatment outcome biomarkers and predictive algorithms challenging (Agid et al., 2011). Some patients improve significantly on a particular antipsychotic, while others can show no response and/or experience adverse side effects with the same antipsychotic. On average, 20% to 30% of SCZ patients do not respond to conventional antipsychotic treatment and less than 40% achieve remission (AlAqeel and Margolese, 2012; Kane et al., 1988). Furthermore, approximately 30% of SCZ patients experience treatment-resistance and clozapine is considered to be the standard treatment for these patients (Meltzer, 1997).

Selection of an appropriate antipsychotic is often via the traditional “trial-and-error” approach, where physicians may prescribe two or three or more antipsychotics in sequence with varying dosages before finding an antipsychotic with acceptable efficacy and tolerable side effects. This procedure is problematic for both the patient and the healthcare system. For the patients, this approach exposes them to the risk of developing adverse drug reactions (e.g., weight gain, tardive dyskinesia (TD)), prolongs their recovery time, and worsens long-term treatment outcome (Perkins et al., 2005). In addition, this “trial-and-error” approach also creates tremendous social and economic burden in various ways, as unsuccessful treatments ultimately lead to waste of medical resources, decrease in labor force participation, and can be a risk to public safety (Cloutier et al., 2016; Kennedy et al., 2014; Pennington and McCrone, 2017).

Due to the possible role of genetic factors in antipsychotic treatment efficacy and side-effects as indicated by previous familial and twin studies, pharmacogenetics has become an important topic of investigation in psychiatry (Mata et al., 2001; Muller et al., 2001; Rahmioglu and Ahmadi, 2010; Vojvoda et al., 1996). Pharmacogenetics investigates how genetic variability influences drug treatment outcomes and offers the potential to provide physicians with an additional tool to create an optimized, personalized treatment plan (Hamburg and Collins, 2010). Pharmacogenetic research that identifies variants associated with antipsychotic treatment response and adverse side-effects has advanced considerably over recent years, moving from candidate gene studies that examine single nucleotide polymorphisms (SNPs) in pharmacokinetic genes, to studies of genes involved in pharmacodynamic pathways. More recent advances include genome-wide association study (GWAS) investigations, the results of which are now being used to generate polygenic risk scores (PRS).

PRS is a statistical method that combines the effects of individual risk alleles across the genome. This approach has demonstrated substantial potential to predict antipsychotic efficacy (International Schizophrenia et al., 2009; Zhang et al., 2019). Additionally, a study conducted by Li et al. (2018) found that SCZ risk variants are related to lurasidone response in a sample with 302 SCZ patients using a polygenic approach. The SCZ risk genes used in the PRS model were related to neurodevelopment, synaptic biology and immune response suggesting that these genes might play a role in antipsychotic response (Li et al., 2018). Furthermore, in an attempt to identify predictors for CLZ-associated phenotypes, such as response, dosage, and metabolic ratio, Mayen-Lobo et al. (2021) conducted an association study in 44 patients with refractory psychosis who received CLZ. The study integrated PRS (SCZ-PRS, Bipolar Disorder (BD)-PRS, Major Depressive Disorder (MDD)-PRS) and analyses with methylome profiles (Mayen-Lobo et al., 2021). The study reported a significant association between BD-PRS and CLZ metabolic ratio and identified two additional nominally significant results between MDD-PRS with CLZ dosage and SCZ-PRS with CLZ response (Mayen-Lobo et al., 2021). However, given the small sample size, the results should be interpreted with caution and future studies with larger sample sizes are warranted. Lastly, epigenetic analyses are increasingly being applied to investigations of medication response in psychiatry and may be combined with genetic information to provide a more comprehensive antipsychotic response prediction in the future (Shah et al., 2015).

Currently, pharmacogenetic test panels for antipsychotic response are not widely used. Similar test panels are being utilized in the treatment of depressive disorders and have support from randomized controlled trials (Bousman and Dunlop, 2018; Bousman and Hopwood, 2016). Epigenetic information has yet to be incorporated into these pharmacogenetic tests. Given this situation, we surveyed the literature to summarize progress and outline the current state of pharmaco(*epi*)genetic research in SCZ. For reviews of pharmacogenetics related to antipsychotic side-effects, see Lally and MacCabe (2015), Meltzer (2017) and Zai et al. (2018).

The purpose of this narrative review is to provide an update on promising pharmacogenetic and pharmaco*epigenetic* studies of antipsychotic response in SCZ, largely focused on research progress since 2014. Since this is a narrative review, it is important to note that all relevant publications cannot be included. Generally, the studies included in our summary tables used larger sample sizes or validated their findings using a replication sample, homogeneous ancestry, and conducted drug-specific analyses. We will discuss the critical issues that need to be addressed in this area and make recommendations for design of future studies that may lead to the development of comprehensive (epi)genetic test panels.

**Section snippets**

**Pharmacogenetics of risperidone**

Risperidone (RIS) is an atypical antipsychotic that is commonly prescribed as a first-line treatment in SCZ. RIS is a potent antagonist of the DRD2 and 5-HT2A receptors that has demonstrated superior efficacy against the positive and negative symptoms of SCZ (Love and Nelson, 2000). Due to its common clinical utilization, many studies have examined the role of genetic variants for association with RIS response. Overall, recent evidence continues to support a role for serotonergic,

**Pharmacoepigenetics**

The investigation of epigenetic modifications and their association with therapeutic antipsychotic medication response may be useful in the discovery of relevant, non-invasive biomarkers to improve personalized psychiatric medicine. The most widely studied epigenetic modification is DNA methylation, but other lesser known modifications include hydroxymethylation, histone modifications, as well as ubiquination, sulfonylation, and non-coding microRNAs (Ptak and Petronis, 2008). Methyl (CH3)

**Pharmacogenetics**

In summary, considerable work has been devoted to identification of reliable biomarkers to predict antipsychotic response in SCZ. Recent findings support both pharmacokinetic genes, such as *CYP2D6*, and pharmacodynamic genes related to conventional dopaminergic and serotonergic neurotransmitter systems. For example, variants within *DRD2*, *COMT* and *HTR2A* have been identified to be associated with antipsychotic response. In addition, there is preliminary evidence for involvement of the

**Conclusions**

Although the FDA currently includes genetic information in its labels for several antipsychotic medications, specific guidance regarding pharmacogenetic testing is not yet provided (Zai et al., 2018). The development of recommendations for pharmacogenetic testing for antidepressants is at a more advanced stage than is the case for antipsychotics, largely due to the fact that much more data and clinical trials are available for antidepressants (Caudle et al., 2017; Hicks et al., 2017). In the

**CRediT authorship contribution statement**

Authors AJL, CCC, AKT, and JLK conceived the content of this review paper. Authors AJL and CCC conducted literature searches and contributed equally to the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

**Role of the funding sources**

This review article was supported through operating grants from the Canadian Institutes of Health Research: Gene Discovery in Schizophrenia (PI: JLK); Ontario Ministry of Research, Innovation and Science (PI: JLK) and Genome Canada GAPP (co-PI: JLK). AKT is supported by the Granville Nickerson fellowship in pharmacogenetics, Brain and Behaviour Research Foundation (NARSAD) and McLaughlin Centre Accelerator Grant (2019–2020). CCZ is supported through Brain and Behaviour Research Foundation (

**Declaration of competing interest**

Dr. Kennedy is an unpaid Scientific Advisory Board member of Myriad Neuroscience USA, and has received speaker honoraria and expenses from Otsuka, Eli Lilly and Novartis, and consultant honoraria and expenses from Roche. Drs. Kennedy and Tiwari are authors on pharmacogenetic related patent applications. CAMH hospital has 15% ownership of Myriad Neuroscience Canada Ltd. There are no conflicts of interest to declare related to this study for the other coauthors.

**Acknowledgments**

None.

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