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EDITORIAL

Towards pharmacogenetic-based treatment in psychiatry

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Introduction

In the era of genomic medicine, there is an emerging demand from patients and providers for better approaches to pharmacological treatment of neuropsychiatric disorders. Pharmacogenetics, the study of how genetic variation affects drug response, is an emerging field poised to transform the way pharmacological treatment is provided. With the collective efforts of numerous expert groups [e.g., Clinical Pharmacogenetics Implementation Consortium (CPIC), Pharmacogenomics Knowledgebase (PharmGKB)], medical centres around the world have implemented pharmacogenetic testing into routine clinical practice. These early successes have reinforced the promise of pharmacogenetics and have ignited further efforts to strengthen the evidence base and understand more deeply how best to implement pharmacogenetics into practice. In this special issue of the *Journal of Neural Transmission*, we are pleased to offer a collection of ten articles that contribute to the current pharmacogenetic evidence base and provide insights on how we may improve clinical implementation of pharmacogenetic evidence. Below we provide highlights of each of the articles according to key objectives of pharmacogenetics.

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Demonstrating the need for pharmacogenetics

When approaching any clinical problem, it is typically wise to get a grasp of the extent to which the problem exists and the potential impact of intervening. In the study by Mostafa et al., they examined actionable genetic variants in *CYP2D6, CYP2C19, CYP2C9* and *VKORC1* within a large Australian population. They concluded that approximately 96% of patients had at least one actionable pharmacogenetic variant. Notably, they also reported a fivefold increase in the frequency of poor metabolizers for *CYP2D6* and *CYP2C19* which was predicted by phenoconversion, i.e. co-medication/substrates which can inhibit *CYP2C19* and *CYP2D6* activities. This highlights the notion that most people are likely to benefit from pharmacogenetic testing and that drug–drug interactions need to be accounted for when interpreting pharmacogenetics test results.

Addressing generalizability

It is well known that findings in one clinical setting do not always apply in other settings and pharmacogenetic findings are not an exception. One factor of paramount concern to the generalizability of pharmacogenetics is ethnicity. The discovery of pharmacogenetic variants for drug response has primarily occurred within European populations, which has raised questions about the applicability of these variants in non-European populations. In this issue, Su et al. examined, in a Han Chinese cohort, the generalizability of a recent European-based genome-wide association between an *ADCKI* genetic variant and paliperidone efficacy. Although they did not find an association with the European variant, they did detect associations with other variants in the same gene, suggesting the *ADCK1* genetic variation may influence paliperidone efficacy across populations.

Maciukiewicz et al. also addressed the generalizability of findings from one ethnic population to another. They examined an important side effect commonly associated

with antipsychotic medication, i.e. antipsychotic-induced weight gain (AIWG). Based on a recent genome-wide association study in Han Chinese patients that implicated two gene variants (rs10977144 and rs10977154) of the protein tyrosine phosphatase receptor type D (*PTPRD*) with AIWG, the authors set out to validate these findings in a cohort of European and African-American patients. Although they did not find an association with the two previously identified variants, they did identify associations with other *PTPRD* variants in both European and African-American patients.

Another factor that can affect the generalizability of pharmacogenetics findings is physical co-morbidities. Amare et al. investigated if the heterogeneity of response to SSRIs in depressed patients is partly driven by co-occurring somatic disorders such as coronary artery disease (CAD) and obesity. Their findings implicate that genetic variants of CAD and obesity are linked to SSRI treatment response in MDD. Important clinical implications to be drawn are that a better SSRI treatment response to SSRIs might be achieved through a stratified allocation of treatment for MDD patients with a genetic risk for obesity/or CAD.

Knowing what we know (and do not know)

Given the volume and speed at which pharmacogenetic and biomarker research is produced, targeted reviews of the evidence are imperative for the field to keep abreast of the current knowledge. In this issue, Busch and colleagues conducted a timely review of genetic, mRNA, and protein markers associated with antidepressant response, with particular focus on monoamine pathways, inflammatory pathways and the hypothalamic–pituitary–adrenal axis. The review highlights many well-known candidates, such as the serotonin transporter and brain-derived neurotropic factor, but also points out several promising candidate markers involved in inflammatory and stress response pathways that if given more research focus may emerge as clinically useful markers.

Addressing risks

Although pharmacogenetic testing is thought to induce less risk for psychological distress compared to prognostic (or diagnostic risk) testing for severe mental conditions, it is important to address risk and benefits of genetic testing of the latter to inform pharmacogenetic testing which might also cause psychological distress to some (e.g., being informed to be a poor metabolizer for *CYP2D6*). Marshe et al. provided a comprehensive up-to-date review article on the clinical implications of *APOE* testing for late-onset Alzheimer's disease (LOAD). Despite much research in this field, benefits and risks of such testing remain controversial. The authors conclude while *APOE* genotyping for LOAD susceptibility provides potential benefits to at-risk patients and can guide changes in positive health-related behaviors; other individuals may experience test-related anxiety, depression and psychological distress. Therefore, more empirical research is required to understand actual psychological and social implications associated with testing.

Capitalizing on opportunities

The implementation of pharmacogenetic testing might be more than just a tool for guiding prescribing. Arandjelovic et al. provide a concise overview of shared decision-making in depression management and propose that pharmacogenetic decision support tools could be used to facilitate this process. Although trials to evaluate pharmacogenetics as a facilitator of shared decision-making have yet to be done, it seems intuitive that pharmacogenetic information could be used to enhance patient engagement and the treatment alliance, in addition to guiding antidepressant prescribing.

Optimizing implementation

Implementation of pharmacogenetics into practice is still in its infancy and research on how best to optimize this process and ultimately increase the utility of pharmacogenetics are welcomed. The article by Menchón et al. examined the role of patient characteristics on the utility of pharmacogenetic testing, an underappreciated area of research within psychiatric pharmacogenetics. Interestingly, they found that easily assessable patient characteristics, such as age, baseline symptom severity, and current depressive episode duration, influenced the utility of the pharmacogenetic test results. Their results reinforce the important contribution of a patient's demographic and clinical information when interpreting and implementing pharmacogenetic test results.

To date, there is limited research examining the utility of pharmacogenetic testing in children and adolescents. Blasco-Fontecilla's study, in this issue, helps to addresses this gap in the research by exploring the pharmacogenetic profiles of children and adolescents with severe mental disorder. Findings from this study suggested that pharmacogenetic testing resulted in clinical improvement as well as reduced side effect burden and the number of medications being taken. These preliminary results are encouraging and will hopefully spur additional research in this area.

Finally, despite the increasing availability of pharmacogenetic testing and dosing guidelines, hurdles to implementing pharmacogenetics into clinical practice remain. In the article by Baskys, several of these hurdles are discussed and helpful

resources for clinicians are provided. The article also advocates for the development of easy to use bioinformatics tools to help prescribers rapidly access and use pharmacogenetics in practice.

Conclusion

Research on pharmacogenetics is advancing rapidly, and implementation of first gene tests has become more and more ubiquitous, and affordable. Moreover, patients and providers alike are recognizing pharmacogenetics as a clinical tool with the ability to complement and advance current standards of psychiatric care. While there are a number of actionable genes (e.g. *CYP2C19, CYP2D6, HLA-A, HLA-B)* and associated consensus guidelines to facilitate tailored prescribing, barriers still remain, some of which have been addressed in this Special Issue. Barriers which remain to be addressed pertain to ensuring adequate education of care-givers, safeguarding against any potential psychological harm being created through testing, and establishing evidence of cost-effectiveness for widespread, pre-emptive pharmacogenetic testing. We believe that the articles contained in this Special Issue, in part, make advances toward addressing these barriers and will hopefully inspire the readership of this Issue to build on the promises and tackle the challenges of pharmacogenetic testing for psychiatric practice.