# CYP2D6 and CYP2C19 genotyping in psychiatry

# CHAPTER 7

Impact of the thesis on the scientific and social community

According to the global burden of disease studies, about 16% of the global population is suffering from a mental disorder or addiction (274). A considerable amount of these patients uses antipsychotic or antidepressant medication. Mental disorders cause considerable burden of disease, in 2016 globally, 162.5 million Disability Adjusted Life Years (DALYs) were lost due to mental or addictive disorders, about 7% of all DALYs lost by disease (274).

In 2017, almost 1.5 million people in the Netherlands, were prescribed an antidepressant or antipsychotic drug (https://www.gipdatabank.nl/servicepagina/open-data). Unfortunately, many of these patients discontinue their treatment because of in-effectivity of the treatment or life-influencing side effects (1,240,241). Patients with SMI, with a long history of antidepressant or antipsychotic drugs, are especially known to suffer from problems with adverse drug reactions and lack of medication effect (1,69,70). Side-effects can impair psychosocial functioning and may influence the quality of life (1,186). There is a need for tools which enhance effectivity and lower the risk on side-effects of pharmacological treatment.
Of specific interest are the activity of the CYP2D6 and CYP2C19 enzymes because about 50-75% of all antidepressant and antipsychotic drugs is metabolized by either one of these enzymes (https://www.gipdatabank.nl/servicepagina/open-data) (29,275). There are studies showing that the activity of the CYP2D6 and the CYP2C19 enzymes is related to the prevalence of side effects and treatment response (6,22). Also, the costs of treatment and length of hospitalization of poor metabolizers (PMs) and ultrarapid metabolizers (UMs) are on average, longer than of intermediate metabolizers (IMs) and normal metabolizers (NMs) (5,42). In a cost analysis study in patients with schizophrenia in Denmark, overall health costs were found to be 177% higher in all extreme metabolizers (PM + UM) compared to NMs and that genotyping could lead to lower treatment costs (7). A study in patients with schizophrenia showed that patients receiving pharmacogenetic testing prior to a switch or start of antipsychotics showed some improvement in side effects compared to the patients receiving treatment as usual, even though effects were minimal and not significant (43). It is hypothesized that CYP genotyping can lead to better treatment outcomes and reduced treatment costs (7).

Precision or personalized medicine may optimize treatment decisions by a tailor-made strategy for each individual patient. Pharmacogenetic testing is becoming more and more available and prices of testing are dropping (276). A genetic test for CYP2D6 and CYP2C19 costs about €260 in an academic hospital in the Netherlands (Erasmus Mc Rotterdam). It is becoming available for a bigger public and psychiatrists are encouraged to perform pharmacogenetic testing. In some hospitals, testing is routine practice, while in others pharmacogenetic testing is seldom done. There are guidelines from the Royal Dutch Association for the Advancement of

Pharmacy available with instruction how to handle with the outcomes of a genetic test, but there are still some issues to address before implementing it in clinical practice.

First, there is a lack of communication between test manufacturers and clinicians, which is required to narrow the gap between the availability and implementation of these tests in psychiatric practice (276). Second, there is still no consensus under psychiatrists if genotyping is (cost) effective and which patient groups could benefit from this diagnostic tool.

This thesis aimed to narrow the gap between evidence from pharmacogenetic studies and clinical psychiatric practice. It is intended to facilitate the clinical working doctor (general practitioners, psychiatrists and all medical doctors prescribing antidepressants or antipsychotics), especially those working with patients with SMI.

We investigated the probability of having a non-normal phenotype in different ethnicities and analyzed whether CYP genotyping could yield better treatment outcomes (psychopathology, side-effects and functioning) for patients with Severe Mental Illness.

In this thesis we introduced a new term: 'non-normal probability estimate'. Introducing this term to the field of pharmacogenomics made it possible to see which ethnicities are at the highest risk for developing dose dependent side effects or treatment failure. The information is presented in world maps, and for the first time it is visualized which world areas are under investigated and have to be focus of research. The prevalence of non-normal CYP2D6 and CYP2C19 phenotypes for the different ethnicities are gathered in two world maps, which is an important step in a globalizing world and may be especially helpful in the treatment of migrants.

We found that 36% of the world population is having a non-normal CYP2D6 phenotype and that 62% is having a non-normal CYP2C19 phenotype. We know now, that to come to a reliable test outcome, one should minimally genotype alleles, that are prevalent in the specific geographic region a patient is from. In inhabitants from the former Netherlands Antilles the same attention should be paid to altered drug clearance, as is paid to Europeans.
Also, we conclude that for patients with SMI on years of antipsychotic treatment, CYP2D6 genotyping is not effective. CYP genotyping did not show any effects on side-effects, psychopathology, functioning or quality of life. Pre-existent high maintenance dosages, irreversibility of side effects and adaptation of the brain to years of D2 receptor antagonism, are possible explanations why genotyping in this population did not show a beneficial effect on one of these parameters. This study is suggesting that routine genotyping in this patient population is not effective and urges to modesty in genotyping. This insight saves us from needless diagnostic testing and pseudo-certainty about medication effects. Although it seems that,

besides extra costs, genotyping is without risk, our study showed that six patients deteriorated after dose adjustment and even two patients had to be admitted in psychiatric hospital because of psychotic decompensation. When following genotyping guidelines without carefully considering clinical symptoms and side effects it could be that genotype guided treatment will do more harm than good. It is highly necessary to study if genotyping in an earlier phase of the disorder, in patients without a long medication history, may be beneficial in terms of effectiveness and side effect profile.
Lastly, we found that the proxy version of the WHODAS 2.0 is a useful instrument for measuring functioning when patients are not able to complete the questionnaire themselves.

The results of the thesis have been published in four scientific journals, of which three are in open access journals and one journal which supplies the article to membered universities or after payment. To inform a broader public of clinicians working in the Netherlands, an article in Dutch will be written and will be submitted to The Journal of Psychiatry.

Individual test outcomes were communicated to general practitioners and pharmacists in the Netherlands and to the psychiatrists at Curaçao. Wherever there were questions about the relevance or practical implications of the test outcomes, they were answered according to the latest scientific knowledge. Findings from the studies were presented at diverse congresses and symposia worldwide. The committee that is writing the Dutch guideline Pharmacogenetics in Psychiatry personally have been informed of the results of the study that shows that routine genotyping in patients with SMI did not show any beneficial effects. Table 1 is summarizing where the research for this thesis was presented. In these meetings, clinicians, fellow researchers and policy makers were informed about the latest results and invited to discuss the possible benefits from genotyping in clinical practice.

Results of the meta-analysis about worldwide prevalence of CYP2D6 and CYP2C19 phenotypes and the non-normal probability estimates, are freely available for a bigger public on the website www.ethnopsychopharmacology.com. This website is an initiative from Prof. M. Braakman and is a platform for scientific data about psychopharmacology and ethnicity.

**Table 1. Congresses at which (preliminary) findings of this thesis were presented**

| DATE | MEETING | TYPE | PLACE |
|---|---|---|---|
| **2014** | ZonMw Diversity congress | oral presentation | The Hague, the Netherlands |
| **2014** | Educational presentation for doctors in training to psychiatrist, Parnassia Group The Hague | oral presentation | The Hague, the Netherlands |
| **2014** | Congress of Dutch Caribbean foundation for clinical higher education (NASKHO) | workshop | Willemstad, Curaçao |
| **2015** | Research day of School for Mental Health & Neuroscience Research (MHENS) Maastricht university | poster presentation | Maastricht, the Netherlands |
| **2016** | Congress of Dutch Association for Psychiatry (NVvP) | poster presentation | Maastricht, the Netherlands |
| **2017** | European Conference of Schizophrenia Research (ECSR) | workshop | Berlin, Germany |
| **2018** | Congress of Dutch Association for Psychiatry (NVvP) | workshop | Maastricht, the Netherlands |
| **2018** | American Psychiatric Association (APA) Research Program | oral presentation+ poster presentation | New York, USA |
| **2019** | Scientific-Educational program of Education Consortium<br><br>Parnassia-LUMC-Rivierduinen | oral presentation | Leiden, the Netherlands |