CYP2D6 and CYP2C19 genotyping in psychiatry

CHAPTER 6

Summary of main findings and general discussion

Summary of main findings

In **chapter 1** we introduced CYP enzymes. The effect of most medication is determined by the rate at which it is metabolized by CYP enzymes in the liver.

In psychiatry, CYP2D6 and CYP2C19 are the most important enzymes. A combination of functional and non-functional alleles is responsible for the activity of these enzymes. There are four phenotype groups: poor (PM), intermediate (IM), normal (NM) (previously referred to as 'extensive'), and ultrarapid metabolizers (UM), which are used to predict whether and how well a drug is metabolized. In this thesis, I have attempted to bridge the outcomes of pharmacogenetic studies with psychiatric clinical practice. The aims and outlines of the different studies in this thesis were described and explained.

In **chapter 2** we reviewed the literature about the prevalence of CYP2D6 and CYP2C19 in different ethnicities worldwide. We translated the predicted phenotypes into a probability estimate of having a non-normal metabolizer status, defined by the prevalence of PM + IM + UM in percentages. The mean probability estimates worldwide are 36.4% for CYP2D6 and 61.9% for CYP2C19, with a very large geographical variation (min-max 2.7-61.2% for CYP2D6 and 31.7-80.1% for CYP2C19). This means that more than half of the world population has a non-normal CYP2D6 and/or CYP2C19 metabolizer phenotype. The world maps show the geographical regions and countries for which information is available, but also highlight the regions with little or no information, especially in Africa and the Middle East.

In **chapter 3** we assessed the prevalence of CYP2D6 and CYP2C19 genotypes in psychiatric patients and in the general population of Dutch Caribbean origin. Arawak's were the native inhabitants of Curaçao. In 1499, Spanish Europeans colonized the island and brought in slaves from West Africa. Immigrants from Latin America and other Caribbean islands came in after slavery was abolished and admixed with the local inhabitants (179). We investigated the impact of this admixture of ancestors on their allele composition and we analyzed if there were differences between psychiatric patients and the general population. In total, 435 individuals were genotyped for CYP2D6 and CYP2C19. No differences in the prevalence of alleles was found between the general population and psychiatric patients. The prevalence of CYP2D6 predicted phenotypes is PM = 5%, IM = 32%, NM = 61% and UM = 2%, and of CYP2C19 predicted phenotypes PM = 2%, IM = 27%, NM = 40% and UM = 31%. This distribution is in fact very similar to that seen in Europeans (188).

In **chapter 4** we tested the hypothesis that dose adjustment to the CYP2D6 phenotype in patients with severe mental illness (SMI) can reduce side effects and improve treatment outcomes in slow metabolizers. If this is true, we would expect

better psychosocial functioning and an increase in quality of life. Of the 269 patients with SMI who were genotyped, we selected all those with a non-normal metabolizer profile and using psychiatric medication metabolized by CYP2D6 (n = 45); 12 of the 45 patients were defined as PMs because they were on CYP2D6 inhibiting medication. We compared them with 45 patients with a normal metabolizer profile. Four months after dose adjustments, patients were examined on the same parameters. Not one of the patients of the dose adjustment group improved in symptoms, side effects, global functioning or quality of life. Six patients deteriorated of whom two patients had to be admitted to the psychiatric hospital because of psychotic decompensation. High maintenance doses, irreversibility of side effects and adaptation of the brain to the changed dopamine levels, are possible explanations for the absence of an effect.

In **chapter 5** we administered the WHODAS 2.0 proxy-administered version in 77 caregivers of patients with SMI so that we could investigate its relationship with psychiatric symptoms, place of treatment, and side effects. The highest scores on the WHODAS 2.0 are found in domains related to interactions with other people and participation in society. Contrary to our expectations, inpatient status appeared to protect patients in their participation/activities in society. This could be because the sheltered environment of a clinic and the associated adjustments in daily activities makes participating in the local society easier.

In patients with a lack of disease insight or severe cognitive deficits, this proxy version of the questionnaire proved useful in gaining more information about their psychosocial disability.

Discussion

After the introduction of antipsychotics and antidepressants in the 1950s, the effectivity of these drugs was demonstrated in numerous double-blind controlled trials (240,241). However, antipsychotics and antidepressants produce several side effects, especially in patients with severe mental illness, who are prescribed these drugs for years and who often have severe side effects. Because there is a wide variability in individual response to standard doses of these drugs, finding the right drug type and dose is a challenging task for the clinician and can take months or even years (6). Pharmacogenetic testing of individual patients for CYP2D6 and CYP2C19 (referred to here as CYP genotyping) could offer more insight into the optimal drug type and dose they require for a good treatment response.

Currently, therapeutic drugs monitoring (TDM) is used to analyze if a dose prescription results in the desired serum level in the blood. It can be argued that genotyping is superior to TDM because it gives a life-long insight into metabolization of medication. However, other factors that can also influence serum levels, are not assessed with genotyping.

So far there has been no conclusive evidence that CYP genotyping is beneficial for clinical outcomes. Pharmacokinetic studies have shown the influence of the CYP2D6 enzyme on serum levels of medication (23,242,243), while relationships between clinical parameters and CYP2D6 activity have also been investigated (21,244,245). Based on these studies, pharmacogenetic guidelines now advise adjusting the dose or changing the medication to fit the phenotype (44,139,246). However there is only scarce evidence to show improvement in clinical outcomes after genotyping (6,27,87). There is, therefore, an urgent need for conclusive advice on using CYP genotyping in psychiatry. In this thesis, we have tried to bridge the gap between the evidence from pharmacogenetic studies and clinical psychiatric practice. We have shown there is a huge variation in phenotypes in different ethnicities, which might explain differences in patients' response to medication. We found, however, no evidence for the clinical relevance of CYP genotyping in patients with severe mental illness (SMI). We conclude that it is still too early to start routine genotyping in this patient population.

"What do I have to do with this?!"

This was the reply from a general practitioner (GP) on receiving the laboratory result with a patient's CYP2D6 and CYP2C19 profile. When we correctly informed pharmacies and GPs about their patients' phenotype (92), it became clear that not all GPs were able to use this information. We informed 132 GPs about their patients' phenotype and after one year we asked if they had adjusted treatment to the phenotype. Only 4 (3%) responded and they had not used the information. This is in line with a 2017 study in the Netherlands that found genotyping results were available to GPs for only 3.1% of the genotyped patients and at pharmacies for 5.9% of their patients (92). In 2014, few psychiatrists were ordering a pharmacogenetic test (91). However, one study on patients with schizophrenia found positive effects of genotyping on their physician's opinion regarding the patient's clinical status (although there was no evidence of improvement of side effects) (89). In 2018 the FDA cautioned that there may be a lack of clinical evidence supporting the utility of clinical pharmacogenetic testing. Although this statement was not agreed on by professionals investigating CYP genotyping in clinical practice (247).

At the start of this PhD project in 2014, it seemed that CYP genotyping was not being adopted in standard psychiatric care and was dependent on the individual preference of the clinician. Until now routine pharmacogenetic testing has not been translated into psychiatric practice (248,249).

Prevalences of CYP2D6 and CYP2C19 worldwide

A review of the literature in 2019 showed that a large percentage of the world population does not has a normal metabolizer phenotype. In chapter 2 we introduced the concept of a probability estimate for having a non-normal phenotype, as defined by the total prevalence of PM+IM+UM. Worldwide, the probability estimates of non-normal metabolizers are 36.4% for CYP2D6 and 61.9% for CYP2C19. There is also a large geographical variation in the prevalences of CYP2D6 (2.7-61.2%) and CYP2C19 (31.7-80.1%). The Mozabite people in Algeria, for example, have a 61% chance of having a non-normal metabolizer phenotype; it is therefore not appropriate to start with them on the same dose of an antipsychotic or antidepressant as a patient from Peru who has a relatively low chance (13%) of having a non-normal phenotype (10). Since 50-70% of antidepressants and antipsychotics are metabolized by one of these CYP enzymes, regular dosing

guidelines will not apply to most patients (https://www.gipdatabank.nl/servicepagina/open-data) (3,4). The observed variation of genotypes between ethnicities worldwide strongly suggests that pre-emptive CYP genotyping should be performed for every patient who will need therapy involving drugs that are metabolized by CYP2D6 and/or CYP2C19 enzymes.

Prevalences of CYP2D6 and CYP2C19 on Curaçao

In one study, we looked in detail at the Caribbean island of Curaçao, part of the former Netherlands Antilles, and where the population is a mix between native inhabitants, immigrants and descendants of former African slaves. Earlier studies there showed that psychiatric patients were vulnerable for developing side effects such as movements disorders and metabolic syndrome (8,65). We hypothesized that this vulnerability might be explained by a higher prevalence of slow medication metabolizers in the population. We therefore determined the prevalences of CYP2D6 and CYP2C19 genotypes on the island and, indeed, found a completely different allele composition than in Europeans, although the translation into predicted phenotypes showed an almost similar distribution between the two groups. These findings imply that, in the Netherlands, the same attention should be paid to altered drug metabolism in immigrant families from the former Netherlands Antilles as is paid to Europeans in clinical practice. Our results also suggested that the inhabitants of Curaçao are mainly an admixture of Europeans and Sub-Saharan Africans, with much less input from Asians.

In addition to the role of its polymorphisms in drug metabolism, it has also been suggested that CYP2D6 contributes to the susceptibility for schizophrenia, because of its role in the biotransformation of tyramine to dopamine (162). In a recent genome-wide association study, CYP2D6 expression was mentioned as a possible risk factor in the development of schizophrenia (250). In our study, we found no differences in CYP2D6 allele frequencies between psychiatric patients and the general island population. There is no evidence that CYP2D6 biotransformation of tyramine into dopamine actually increases susceptibility for schizophrenia. One explanation could be that studies that found lower percentages of poor metabolizers (PM) in patients with schizophrenia might have compared a selected inpatient group with healthy outpatient volunteers, which biased the results (67). In our study, almost 30% of our psychiatric population were outpatients, so the chances of bias were lower. Moreover, because our control group was from the same mixed ethnic background, our results were not affected by ethnic differences. We found no poor metabolizers of CYP2C19 in the psychiatric patients, in contrast to 4.1% in the volunteers from the general Antillean population. But because the *2 allele, which causes the PM phenotype (*2/*2), was equally prevalent in both groups (14.7% vs.

16.2%, p = 0.595), we think this finding is coincidental. The absence of poor metabolizers of CYP2C19 has also been reported in Panamanian Indian and Mexican populations (182,183). The Indian heritage in the Netherlands Antilles could explain the low prevalence of CYP2C19 PM among our subjects. There is no convincing relationship between CYP2C19 and psychiatric symptoms (46).

Analyzing functioning in patients with SMI using WHODAS 2.0

While investigating the prevalence of CYP genotypes in the population of Curaçao, we also assessed the psychosocial functioning of those patients with severe mental illness (SMI). For years, treatment of psychiatric patients with severe psychiatric disorders has focused on their symptoms. The main treatment aim was remission of psychotic symptoms and behavioral problems. This approach is, however, not necessarily associated with better disease outcomes over time, since symptomatic remission is only partly connected to social functioning and quality of life (251). In recent years, treatment has focused on recovery, in which the most important goal is to regain a meaningful life in the community, including being able to participate in worthwhile activities and fulfilling social roles (205–208). We assessed the psychosocial functioning of patients with SMI using the World Health Organization Disability Assessment Schedule (WHODAS 2.0)(252).

Contrary to our expectations, we found that inpatients had fewer problems in participating in society than outpatients. We suggest being in the sheltered environment of a psychiatric hospital, with its associated adjustments in daily activities, may encourage participation in society. For example, nurses wake patients as part of their daily routine and help them attend creative and social activities organized by the hospital. Inpatients know each other and are mutually tolerant.

Another possibility is that inpatients and their healthcare professionals are accustomed to the status quo and may have lower expectations from life than outpatients (and their healthcare professionals) who are constantly confronted with their disabilities when in contact with society. These different frames of reference could partly explain the higher level of disfunction amongst outpatients.

Another important finding was the relationship between side effects and psychosocial functioning. Particularly drug-induced parkinsonism was associated with a broad spectrum of psychosocial disabilities, such as getting around and performing household activities. This is good reason for psychiatrists to pay more attention to the effect of adjusting dose to the CYP2D6 phenotype, in patients with parkinsonism.

Effectivity of CYP2D6 genotyping

In our patients with SMI on Curaçao, we also planned to investigate the effectivity of CYP genotyping on treatment outcomes. At the start of the project, we intended to evaluate dose adjustments to the CYP2C19 phenotype as well. Although about 60% of our patients had a non-normal CYP2C19 predicted phenotype, we were not able to include any in our study who needed a dose adjustment according to the guidelines (there were no patients with a non-normal CYP2C19 phenotype using medication metabolized by the CYP2C19 enzyme). CYP2C19 genotyping therefore had no added value in this group. In other populations, where patients are mainly prescribed medication metabolized by the CYP2C19 enzyme, genotyping may well predict response in certain individuals, but it is not yet clear if this will translate to better clinical outcomes (253).

Before we could make dose adjustments to the CYP2D6 phenotype, we had to find out if psychiatrists had already adjusted doses because of side effects or treatment resistance. By recalculating the medication doses to a Defined Daily Dose (DDD), we found that the average DDD in the whole group was 1.68 (SD 0.92). There was no correlation between the predicted phenotypes and the prescribed dose of antipsychotics (Figure 2, chapter 4), PMs, IMs and UMs were prescribed the same amounts of psychopharmacological medication as the NMs, even when we only included antipsychotics metabolized by the CYP2D6 enzyme. We even found higher doses of antipsychotic medication in slow metabolizers (PM 1.86 (SD 1.21) vs. UM 1.12 (SD 0.44), $p = 0.16$) (Figure 2, chapter 4), and again when we analyzed the DDD of medication metabolized by the CYP2D6 enzyme.

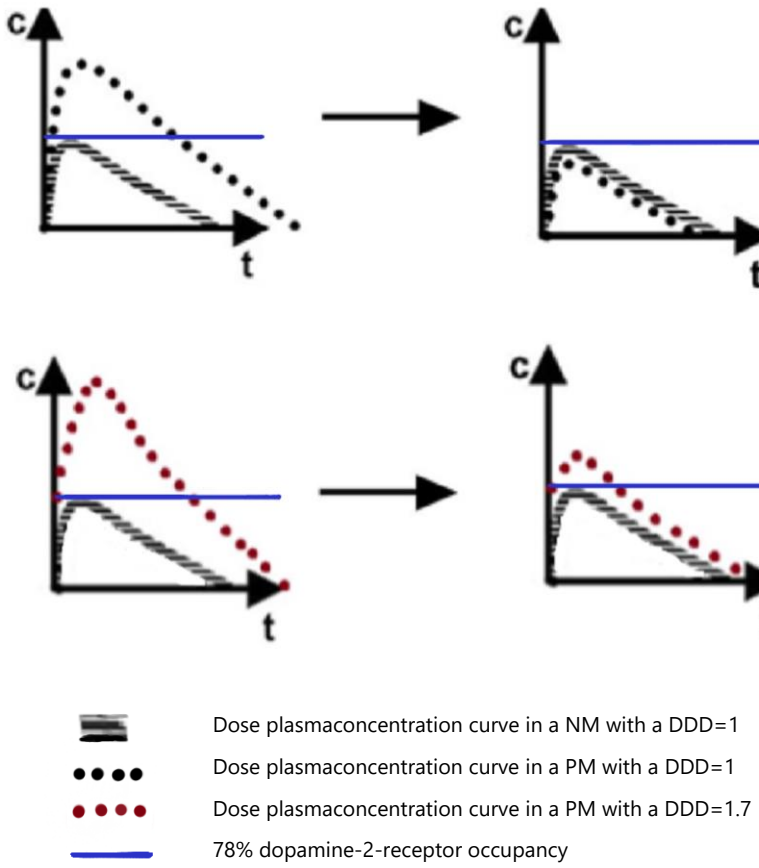
In a Russian study of inpatients with schizophrenia, there were also no differences found in mean dose of antipsychotic medication between the CYP2D6 metabolizer groups with an average DDD ~ 1.7 (254). In a Swedish study, significantly lower doses of antipsychotics were found in PM- than EM outpatients. This could be due to a lower average prescribed DDD in this group of patients (DDD = 0.6), which would make any differences in the effects of medication more clear than in patients on higher doses (255).

When we compared the in- and outpatients in our population, we found a DDD = 1.8 in the inpatient group versus a DDD = 1.2 in the outpatient group ($p<0.001$). In the outpatient group, we did not find a correlation between CYP2D6 activity level and DDD. Apparently, the clinical differences seen in tardive dyskinesia and parkinsonism are not large enough to stimulate psychiatrists to adjust dose to an individual phenotype. Our results also confirmed this: we found no differences in drug-induced movement disorders nor in metabolic parameters between the different metabolizer groups. Thus, it is even more important to study whether CYP

genotyping and medication adjustments actually result in better treatment outcomes.

Many antipsychotics, especially those metabolized by CYP2D6 (haloperidol, aripiprazole and risperidone) have bell-shaped dose-response curves, which means that treatment response decreases if the dose is are higher than optimal (256). With these types of antipsychotics, PMs automatically have a higher chance of being prescribed a dose above the optimal one for them and therefore a lower treatment response. Also, higher plasma levels of antipsychotic medication show lower levels of subjective wellbeing in patients with schizophrenia (257). Positron emission tomography (PET) studies showed that when dopamine 2 receptor occupancy exceeds 78%, the likelihood of extra pyramidal symptoms is significantly increased, whereas an occupancy between 60-70% is optimal in patients with schizophrenia (41,157). It could be that doses were far above the 78% occupancy even after dose reduction and that might explain why we found no differences in symptoms between the two groups (Figure 1). Some studies found differences in tardive dyskinesia and parkinsonism between patients with a normal (NM) and a reduced metabolism (PM + IM). Patients in these studies were also taking antipsychotic medication long term, but again in significantly lower doses (DDD = 0.3-1) (43,160,258,259).

Figure 1. Schematic adaptations of the dose concentration relationship, after a single dose of antipsychotic medication, before and after 50% dose reduction



DDD= Defined Daily Dose, c=concentration of drugs in blood, t=time in hours

Most of the studies on movements disorders between metabolizer groups were underpowered and the results did not reach significant difference. When the results were pooled in a meta-analysis, the differences in severity of drug-induced movement disorders were considered too small to be clinically meaningful (OR = 1.24) (27,160,258–260). We also found no differences at the start of our study, nor a trend toward improvement after dose adjustment. Even in a subanalysis of 16 patients using small doses (DDD ≤ 1.0), we saw no improvements in the intervention group. This supports the idea that differences in movements disorders between

metabolizer groups are too small to be demonstrated in small clinical trials or in clinical practice.

Another explanation for the lack of effect from CYP genotyping on psychiatric symptoms or side effects could be that long-term use of antipsychotics induces structural changes in the brain (132). In a review, the process of sensitization and tolerance to antipsychotics was proposed to explain why clinical trials fail to demonstrate efficacy of novel treatments (261); and chronic use of antipsychotics induced changes in neuroplasticity and the patient's brain became sensitive to antipsychotic medication (262). Sensitization leads to increased behavioral side effects. A prior antipsychotic treatment history and subsequent withdrawal because of dose adjustment could cause a 'supersensitivity psychosis', i.e. a drug-induced psychotic relapse following an interruption of chronic antipsychotic treatment. The drug-induced increase in the mesolimbic dopamine postsynaptic D2 (high) receptors, which has been shown in animal models, is suggested to be the underlying mechanism (263). A Japanese study has shown a higher prevalence of supersensitivity psychosis in CYP2D6 poor metabolizers, although the results did not reach significance. They hypothesized that a higher risperidone concentration in PMs leads to a higher risk of this type of psychosis (264). The supersensitivity psychosis might explain the deterioration of some patients after dose adjustment in our study sample (n = 6).

Liu and Takeuchi have recently proposed an algorithm for dose reduction of antipsychotics with only a fraction (no more than 25%) of the dose to be reduced at any time, and with at least a 6-month stabilization period to prevent psychotic decompensation (265). This is in marked contrast with the 50% dose reduction, taken in two steps over 4 months, we adopted in our study setting.

More support for this sensitivity hypothesis is that drug-induced movement disorders are not as reversible as initially thought. Earlier studies reported that only 3% of patients who discontinued the drugs causing their movement disorder showed improvement in tardive syndromes (133). A lower dose of antipsychotics did not decrease the severity of parkinsonism in patients with SMI on high doses (66). In this clinical population, perhaps a dose adjustment to match their CYP2D6 phenotype would have had an effect in an earlier phase of treatment, but the years had led to irreversible neuroplastic changes.

When we searched the literature, we found most of the studies reporting potential clinical benefits from CYP genotyping were observational; they found extreme metabolizers had longer stays in psychiatric hospital (5,42,138,266). We found only three prospective studies that reported an effect of CYP genotyping on side effects for patients with schizophrenia with non-normal CYP2D6 metabolizer profiles (7,43,254). There were two differences between these studies and our study. First, in

two studies reporting on the average dose of antipsychotics, the average DDD was around 1 compared with DDD = 1.68 in our population. Second, in all three studies, patients were selected for CYP genotyping when there was an intention to start antipsychotic treatment or to switch drug type, and clinical reasoning was part of the decision to adopt genotype-guided treatment. In the study by Herbild et al., for example, there was only the additional information on the patient's genotype and a recommendation to adjust the pharmacological treatment accordingly, but the decision adjust the dose was left to the clinician. Our study was different in the timing and instructions on dose adjustment: there was no clinical reason to genotype the patients and the dose reductions were purely guided by genotype and not by the patient's clinical symptoms. Many of the patients in our study who received adjustments were already relatively stable on their dose regimes, although their doses were high, they were suffering from diverse side effects, and many were admitted to psychiatric wards for chronically ill patients.

This means that in other studies finding an effect of CYP genotyping, there was already a clinical reason or intention to change from standard dosing regimens. These patients were not stable on their dosing regimens or were suffering from so many side effects that they had already requested a change in medication. In our study, every patient's dose was adjusted, clinical symptoms were not taken into account. We excluded only those patients who were unwilling to have their dose adjusted (n = 3). It is possible that a selected group of patients who do not respond on standard treatment regimes would see more benefit from genotype-guided treatment. This could be revealed when there is a reassessment of the standard treatment and/or when clinical pros and cons are being carefully weighed. The large group of patients who benefit from standard treatment without too many side effects would not necessarily benefit more from genotype-guided treatment and dose adjustments. In 15% (6/45) of the patients we investigated adjusting the dose even caused their condition to deteriorate.

Pharmacokinetics

The majority of evidence for CYP genotyping in pharmaceutical guidelines comes from studies on the relationship between CYP activity and the plasma concentrations of psychiatric medication (267–269). The relationship between the plasma concentration of antipsychotic medication and clinical outcomes is a topic of ongoing debate. For example, some studies found no correlation between plasma concentration of active moiety and clinical efficacy of risperidone (270,271).

We were able to measure the plasma levels of haloperidol, zuclopenthixol and risperidone in 31 patients at the start of the study. Only for risperidone was there a moderate correlation between metabolic activity and plasma level (Pearson

correlation coefficient -0.5; p = 0.08) (with higher plasma levels in PMs than in NMs and UMs). This is in line with another study that found a correlation between risperidone concentration and CYP2D6 activity (272). However, it is in contrast with studies in natural cohorts of patients with schizophrenia that found correlations between haloperidol and zuclopenthixol plasma levels and CYP2D6 activity (22,258). It should be noted that, in those studies, body weight and smoking were equally important determinants of haloperidol clearance.

Conclusions

Since 1988, more than 3000 papers on CYP2D6 and/or CYP2C19 have been published. Probability estimates of a person having a non-normal metabolizer profile show that about 36.4% (CYP2D6) and 61.9% (CYP2C19) of the world population has a non-normal metabolism, which suggests that genotyping may be highly relevant to clinical practice. This is supported by pharmacokinetic studies. However, these studies have mostly been conducted by pharmacologists and pharmacogeneticists, and they do not offer translation of genotyping results to clinical practice. This thesis has attempted to bridge the gap between the evidence from pharmacogenetic studies and psychiatric practice.

The majority of the evidence for current treatment guidelines comes from studies on the relationship between CYP activity and plasma levels of psychiatric medication (267–269). Although plasma levels are clinically relevant, the 'proof of the pudding' is if genotype-guided treatment results in more effectivity and/or fewer or less severe side effects.

Studies showing trends in clinical validity in patients with SMI are often underpowered. Patient groups on lower doses of antipsychotics seem to benefit the most from genotype-guided treatment. There is also some evidence that CYP2D6 and CYP2C19 genotyping, as additional information next to clinical considerations, can benefit treatment outcomes (psychopathology and side effects).

Although it might appear that genotyping is without risk, our study of 45 patients showed that six deteriorated after their dose was adjusted, including two who had to be admitted to a psychiatric hospital because of psychotic decompensation.

It could be that in patients on years of antipsychotic treatment, following genotyping guidelines without carefully considering clinical symptoms and side effects, will do more harm than good.

Directions for further research

The results of this thesis call for modesty regarding the benefits of genotyping in patients with severe mental illness. Future studies should focus on the clinical utility of CYP genotyping in psychiatric practice. First, patients with SMI have often been using antipsychotic medication for several years. Irreversible neuroplastic changes in the brain might explain the negative results for CYP genotyping in our study. It is therefore necessary to study if genotyping should be used at an earlier phase of the disorder, in patients without a medication history. It might even prevent the development toward SMI. Future studies should be performed prospectively and focus on patients with a first psychotic episode, with a blank or short history of antipsychotic use.

Second, studies providing evidence for cost effectiveness show that differences between metabolizer groups only become significant when patients using medication not metabolized by CYP2D6 are excluded from the analysis (42). Studies also easily become underpowered when patients with a normal metabolizer phenotype are included in the analysis (7). This means that to be able to estimate effects of routine CYP2D6 genotyping, the studies should include large numbers of patients using medications metabolized by CYP2D6.

In the Netherlands, antipsychotics metabolized by CYP2D6 (haloperidol, risperidone, aripiprazole and zuclopenthixol) form 41% of that medication prescribed (https://www.gipdatabank.nl/servicepagina/open-data)(2017). In about 36% (PM + IM+ UM) of these patients (273), the Royal Association for the Advancement of Pharmacy would advise adjusting the dose to phenotype (44,85). Thus, if all patients using antipsychotics are genotyped for CYP2D6, around 15% (0.41*0.36) of them may benefit from dose adjustment. This means that about seven patients have to be genotyped for one patient to benefit from genotype-guided dose adjustments in one patient, or in other words, the number to screen is seven.

Large randomized controlled trials are therefore needed. Confounders such as inhibiting medication, treatment adherence, drug and alcohol use, and inflammation should be considered and drug-plasma levels should be measured. When evaluating the outcomes, the focus should not only be on primary disease symptoms and side effects, but also on recovery of function. In patients with cognitive deficits or lack of disease insight, the WHODAS 2.0 proxy version proved to be a powerful clinical instrument.

Lastly, research on genotype frequencies should focus on regions that are under-investigated such as the Middle East and Africa. When individuals are included in a study, their ethnicity must be well defined, preferably by confirming three generations of lineage. Most importantly, a minimum number of alleles and

duplications must be investigated to avoid overestimation of the wildtype/normal phenotype.

This thesis shows there are many studies that hold value for clinical practice, but the field would benefit from much more communication between the disciplines to make evidence from the laboratory useful for patients in clinical practice.