REVIEW

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CYP2C19 polymorphism in relation to the pharmacotherapy optimization of commonly used drugs

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Purpose: The CYP2C19 isoenzyme plays an important role in the efficacy and safe use of many drugs. The aim of this review is to demonstrate how *CYP2C19* mutations influence everyday patient treatment, leading to adverse drug reactions or therapy failure in many common diseases. *Methods*: A PubMed literature search was performed on clinical publications evaluating the impact of *CYP2C19* on pharmacotherapy outcome. Main fields of medicine with strong outcome dependency on the *CYP2C19* genotype were selected. We also focused on clinical recommendations for the use of drugs referring to *CYP2C19* polymorphism. *Results:* The fields of medicine where clinical outcome particularly depends on *CYP2C19* polymorphism are gastroenterology, cardiology, psychiatry, mycology and oncology. CYP2C19 is involved in proton pump inhibitors metabolism, thus it can influence reflux therapy, ulcer prevention and *Helicobacter pylori* eradication treatment. The CYP2C19 enzyme plays also a vital role in the two bioactivation steps of clopidogrel leading to lower (*CYP2C19*17* carriers) or higher (*CYP2C19*2* carriers) risk of major adverse cardiovascular events. It affects the antidepressant treatment and methadone replacement therapy as well as voriconazole prophylaxis. The presence of a *2 allele is associated with longer relapse-free time or better survival, and the *17 allele with more favorable outcomes in breast cancer patients treated with tamoxifen. *Conclusions*: Knowledge of the *CYP2C19* polymorphism could positively affect individual treatment and lead to better patient outcomes in many cases. The introduction of pharmacogenetic testing into medical practice would be a good way to minimize negative outcomes of therapy, and to reduce unnecessary medical costs.

1. Introduction

The efficacy, as well as safety, of pharmacological treatment depends on numerous factors. Some of them, extrinsic factors, are connected with the pharmaceutical, pharmacokinetic, and pharmacodynamic properties of medications and drug interactions, while intrinsic factors belong to the patients, e.g. age, gender, pregnancy, genetic factors, disease states, organ dysfunctions and race/ethnicity. They lead to significant inter- and intra-patient variability in drug response with regard to optimal doses and adverse drug reactions (ADRs). Optimization of therapy requires an understanding of the relationship between these factors. However, genetic variation can account for as much as 95% of variability in drug disposition and effects. There are numerous examples of inter-individual differences in drug response caused by common genetic variations (called polymorphisms) in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets (Yusoff et al. 2015; Caudle et al. 2017).

The CYP2C19 cytochrome P450 isoenzyme belongs to family 2, subfamily C, polypeptide 19. It is predominantly expressed in the liver but lower levels of the enzyme can be found in the small intestine (Läpple et al. 2003). It is involved in the biotransformation of several drugs which are important in clinical practice, and are presented in table 1 (Dolton and McLachlan 2014; Flockhart Table™; Hicks et al. 2017; Hokari et al. 2001; Kattel et al. 2015; Li et al. 2013; Li-Wan-Po et al. 2010; Wang et al. 2013).

The encoding *CYP2C19* gene is located on chromosome 10q24.1-q24.3 and is highly polymorphic, with over 49 variant alleles (www.pharmvar.org). Only 12 of them have a determined influence on *in vivo* enzymatic activity. Based on the results of phenotyping, patients are stratified as normal (NMs), intermediate (IMs), poor (PMs), rapid (RMs) and ultrarapid (UMs) metabolizers. Their enzymatic activity varies according to the number of *CYP2C19* loss of function (LOF) alleles. Homozygous wild-type *CYP2C19*1* has full drug-metabolizing capacity. Poor metabolizers usually possess two null alleles, such as **2A, *2B, *3A, *3B, *4A, *4B, *5A, *5B, *6, *7, *8*. Among them *CYP2C19*2* and *CYP2C19*3* are the most common and main causative alleles for slow drug metabolism. PMs may suffer unwanted adverse effects with normal doses of drugs inactivated by CYP2C19, and may also show weak responses to drugs that need to be activated by this isoenzyme. By contrast, *CYP2C19*17* showed increased gene expression and enzyme activity, with the consequence of a lack of response to certain drugs (see Table 1) (Ang et al. 2016; Caudle

Table 1: Selected substrates for CYP2C19 isoenzyme

Major drug classes	Drug examples
Proton pump inhibitors	Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Antiplatelet	Clopidogrel
Antidepressants TCAs	 Amitryptyline, clomipramine, imipramine
SSRIs	Citalopram, escitalopram
Anxiolytics	Clobazam, diazepam
Analgesic	Methadon
Antifungal	Voriconazole
Anti-oestrogen	Tamoxifen
Antiviral	Nelfinavir

TCA - tricyclic antidepressants, SSRI – selective serotonin reuptake inhibitors

Table 2: *CYP2C19* diplotype-phenotype relationship

Phenotypes	Frequency of patients in different ethnic groups (%)	Genotype	Examples of diplotypes/alleles	Enzyme activity
Normal metabolizers (NMs)	8.6^{O}-47.4^{A}	Combination of normal function alleles	*1/*1	Full - normal
Intermediate metabolizers (IMs)	24.1^{AF}-47^{EA}	Combination of normal, decreased, and/or no function alleles	*1/*2, *1/*3	Intermediate (activity between normal and poor metabolizer)
Poor metabolizers (PMs)	2^{A}-14.5^{EA}	Combination of no function alleles and/or decreased function alleles	*2/*2, *2/*3, *3/*3	Low or absent
Rapid metabolizers (RMs)	1.5^{O}-27^{C}	One copy of a normal function allele and one copy of an increased function allele	*1/*17	↑ compared to normal metabolizers
Ultrarapid metabolizers (UMs)	0^{EA}-4.6^{C}	Two increased function alleles	*17/*17	↑ compared to normal metabolizers

O-Oceanian, A-American, AF-African, EA-East Asian, C-Caucasian

et al. 2017; Ding et al. 2015; Hicks et al. 2015; Kim et al. 2017; Lee 2013; Obeng et al. 2014; Spina and de Leon 2016; Yusoff et al. 2015). Main information on genotype-phenotype relationship is presented in Table 2 (www.pharmgkb.org).
The aim of this review is to demonstrate how *CYP2C19* polymorphisms influence everyday patient treatment, leading to adverse drug reactions or therapy failure in the treatment of many common diseases.

2. Study design

We performed a PubMed literature search on clinical publications evaluating the impact of CYP2C19 on pharmacotherapy outcome. We included articles published between 2013 and 2018. We laid our main focus on original and review papers. Main MeSH terms used as keywords to search articles published in English were "CYP2C19", "polymorphism", "mutation", "drug therapy", "guideline". Different styles of the search terms were also used in order to obtain every relevant paper. On the basis of collected data we determined five general fields of medicine where *CYP2C19* mutations have the greatest impact on therapy outcome. Those were gastroenterology, cardiology, psychiatry, mycology and oncology.

2.1. Impact on gastroenterology

CYP2C19 is involved in the metabolism of proton pump inhibitors (PPIs), thus it can influence reflux therapy, ulcer prevention and *Helicobacter pylori* eradication treatment. It was first reported by Furuta et al. (1998), who stated that *H. pylori* eradication rates in normal metabolizers of PPIs are lower than in heterozygote normal and poor metabolizers. The *CYP2C19**2 loss of function allele is associated with decreased PPI clearance, resulting in more active PPIs. Standard doses of the aforementioned drugs may lead to higher exposure to them and improved treatment outcomes. In contrast, individuals with increased *CYP2C19* activity may have an insufficient response to treatment as the active drugs are inactivated at a faster rate. The Ichikawa et al. (2016) meta-analysis confirmed that rapid metabolizers with reflux esophagitis have an increased risk of being refractory to PPI therapy compared with poor metabolizers.
A study carried out by Gawrońska–Szklarz et al. (2012) suggests the strong influence of *CYP2C19* polymorphism on pantoprazole pharmacokinetic properties among the Polish population. 57% of inter-subject variability in pantoprazole clearance may be explained by *CYP2C19* genotype status. Deshpande et al. (2016) conducted research among healthy Indian volunteers and found that ultra-rapid metabolizers had the lowest AUC (area under the curve) values for pantoprazole and esomeprazole out of all the established genotypes. The best response to pantoprazole therapy was found in the group of patients demonstrating the *CYP2C19**2 allele and to esomeprazole in *wild type* individuals, where the highest concentrations of the aforementioned drugs were observed.
As for *Helicobacter pylori* eradication, a meta-analysis carried out by Padol et al. (2006) showed a correlation between the success of eradication treatment and CYP2C19 genetic variation when omeprazole is used in dual or triple therapy regimens. One study reported that when using omeprazole as part of treatment to eradicate *H. pylori*, success was achieved in all patients who had little or no CYP2C19 activity, but in only 29% of patients who had normal CYP2C19 activity. No correlations for lansoprazole or rabeprazole could be determined in the research (Padol et al. 2006). Studies conducted by Phiphatpatthamaamphan et al. (2016) support the finding that *CYP2C19* polymorphism has no influence on the success of triple therapy with rabeprazole.
According to these findings most authors postulate the need for CYP2C19 genotyping in order to perform dosage regimen adjustments of PPI among patients treated with omeprazole and pantoprazole (Deshpande et al. 2016; Gawrońska-Szklarz et al. 2012; Kuo et al. 2014). The FDA-approved drug label does not comment on dose adjustments based on the genotype, but the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) recommend an increased, by even 100-200%, dose of omeprazole and a 50-100% increased does of esomeprazole for the eradication of *H. pylori* in UMs. For other indications an increased dose should be considered (Dean 2012a, b). There are also newer ongoing studies that are evaluating the benefits from genotyping enrollment in PPI prescribing in adult and pediatric populations (Rouby et al. 2018).

2.2. Impact on cardiology

Clopidogrel is an example of a commonly used medication in cardiology where knowledge of the pharmacogenomic profile of a patient may have a profound impact on outcomes. It is a thienopyridine antiplatelet prodrug, used in the prevention of atherothrombotic and thromboembolic events in atrial fibrillation. To achieve a pharmacologic mode of action, clopidogrel has to be metabolized to its active form – a thiol derivative. The CYP2C19 enzyme plays a vital role in the two bioactivation steps of clopidogrel by participating by 44.9% in the first step and 20.6% in the second one. The other hepatic CYP450 enzymes which are involved in these processes include the CYP1A2 and CYP2B6 in the first step and the CYP2B6, CYP2C9, CYP3A4/5 in the second step (Amin et al. 2017; Caudle et al. 2014; Ding et al. 2015). Clinical studies of platelet function have shown that 16 to 50% of patients may have resistance or be nonresponders to clopidogrel treatment. This may lead to ischaemic events, and the patient's death. Many genetic and nongenetic factors are considered to be significant contributors to this observation. The recommended doses of clopidogrel are less effective in patients with loss of function variant alleles (*CYP2C19**2-*8*). Compared with normal metabolizers (*CYP2C19**1/*1*), these patients are more likely to be hypo-responsive to clopidogrel due to decreased inhibition of platelet aggregation and at increased risk of major adverse cardiovascular events, e.g. heart attack, stroke or death. It was found that less CYP2C19

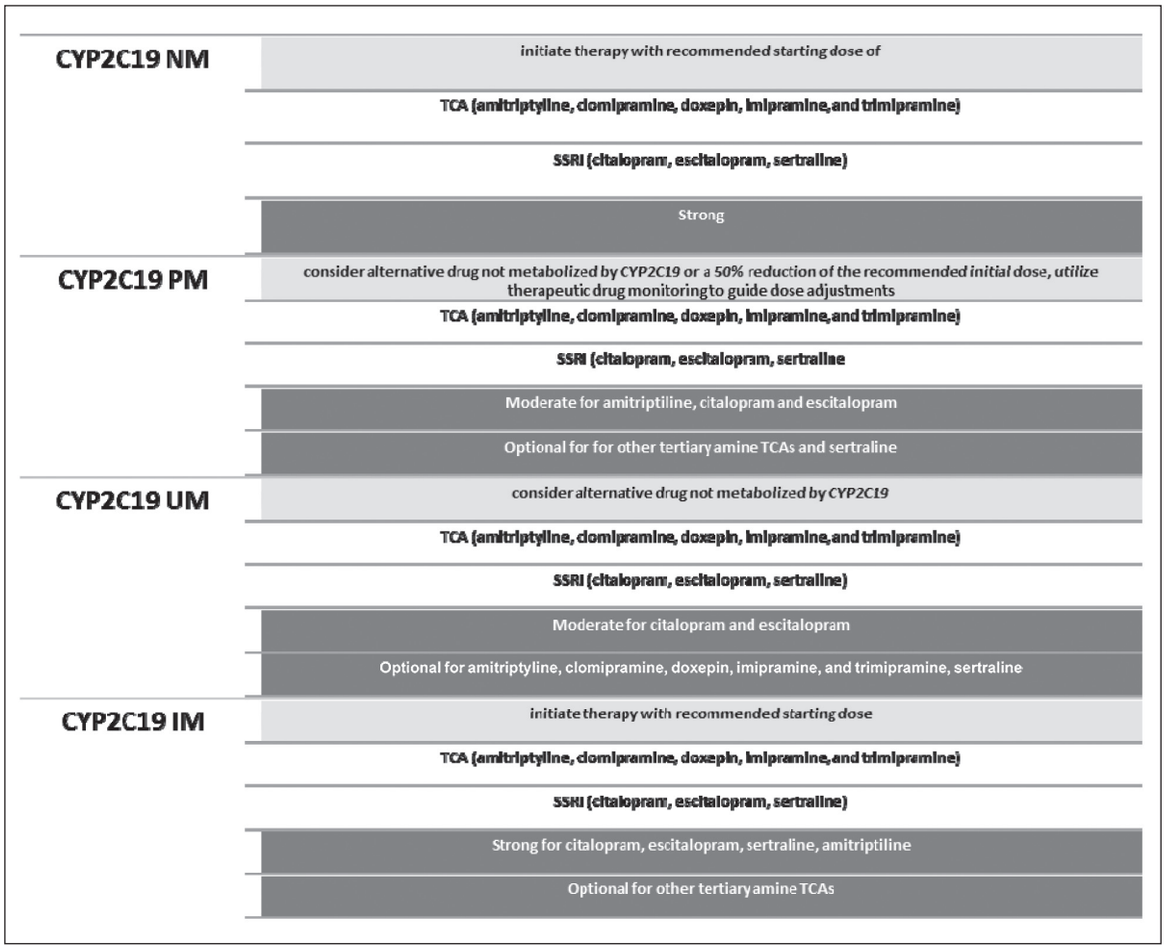

Fig. 1: Genetic recommendations for tricyclic antidepressant and selective serotonin reuptake inhibitors use according to the Clinical Pharmacogenetics Implementation Consortium Guidelines (CPIC)

activation leads to a reduction in active metabolites, which results in a decrease in suppressive effect on platelet aggregation. Heterozygous and homozygous *CYP2C19*2* have 1.55 and 1.76 greater risks, respectively, of major cardiovascular diseases than homozygous wild-type *CYP2C19*1* with normal enzyme activity. The likelihood of stent thrombosis is also increased, by 2.67 times in the heterozygous variant and by 3.97 times in the homozygous variant. It has been shown that the AUC of clopidogrel is approximately 3 times higher in PMs than in NMs. In addition, the AUC of the active metabolites of clopidogrel in PMs are approximately 30% lower than those in NMs. Based on this information, the inhibition of platelet aggregation by an antiplatelet drug in PMs would be 10–30% lower than that in NMs. It was found that patients demonstrating a minimum of one *17 allele are at higher risk of major bleeding events during clopidogrel treatment after stenting. Additionally patients demonstrating at least one loss of function allele have higher in-treatment platelet reactivity, which in some cases leads to therapy failure (Amin et al. 2017; Choi et al. 2016; Kim et al. 2017). Studies performed among the Asian population showed a correlation between the *CYP2C19*2* allele and resistance to clopidogrel in cerebrovascular diseases, which may also be valued as a predictive factor for therapy success (Cervinski et al. 2013; Mega et al. 2009; Sen et al. 2014; Yi et al. 2016). Simon et al. (2009) showed that *CYP2C19* loss-of-function allele carriers demonstrate a higher rate of subsequent cardiovascular events e.g. myocardial infarction then non-carriers.

Looking for a solution to this clinically relevant problem, Cervinski et al. (2013) established a CYP2C19 genotyping assay for everyday use. The limitations of this method are: the possibility of detecting only *2, *3 and *17 alleles, the lack of distinction between the *2 and the *10 alleles, located near the loss of function allele, and the low number of patients already tested. Only 30 patients without confirmation of their genotype via sequencing were examined in the study. Nonetheless the attempt to evaluate such an assay underlines the need for genotyping enrollment in clopidogrel treatment. In 2010, the United States (US) Food and Drug Administration (FDA) put a black box warning on clopidogrel to make patients and practitioners aware that PMs are at high risk of failure. The FDA-approved label for clopidogrel (Plavix®) was updated in September 2016 and warns that patients who are CYP2C19 poor metabolizers may experience diminished effectiveness of the drug as compared to patients with normal CYP2C19 function. The drug label suggests that a different platelet P2Y12 inhibitor be used in patients identified as CYP2C19 poor metabolizers. Routine clinical use of genotyping is not recommended by, e.g. The Society for Cardiovascular Angiography and Interventions (SCAI). In contrast the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends considering, for PMs or IMs, the administration of prasugrel or ticagrelor (Amin et al. 2017; Choi et al. 2016; Kim et al. 2017; Pereira et al. 2016; Scott et al. 2013).

2.3. Impact on psychiatry

CYP2C19 genotype also plays an important role in psychiatry, not only in antidepressant treatment but also in methadone replacement therapy (Dean et al. 2012c; FDA clobazam annotation; Hicks et al. 2015, 2017; Mouly et al. 2015; Mrazek et al. 2011; Spina and de Leon 2016; Vasudev et al. 2017; Wang et al. 2013). Tricyclic antidepressants (TCAs) (amitriptyline, imipramine, clomipramine) and selective serotonin-reuptake inhibitors (SSRIs) (citalopram, escitalopram, sertraline) are metabolized in the liver mainly by the CYP2C19 enzyme (Hicks et al. 2015; Spina and

de Leon 2016). Amitryptyline biotransformation results in active metabolites, including nortriptyline, and imipramine - desipramine. These are also TCAs. The extent of this process decreases in poor metabolizers. In their representatives, standard doses of tertiary amines lead to higher plasma levels of parent compounds and lower levels of metabolites, and serotonin reuptake inhibition is more pronounced. Some common ADRs of TCAs are anticholinergic, central nervous system and cardiac effects. Rapid and ultrarapid metabolizers are at risk of low plasma levels, imbalance between the parent drug and metabolites, and as a consequence treatment failure and/or adverse reactions. The *CYP2C19*17* allele is associated with increases in nortriptyline and desipramine levels (Hicks et al. 2017; Spina and de Leon 2016).

Inter-individual differences in the pharmacokinetics of SSRIs and treatment outcomes are also associated with *CYP2C19* polymorphism. A study carried out by Mrazek et al. (2011) showed that patients with a non-psychotic major depressive disorder who were treated with citalopram and expressed the *CYP2C19*2* allele had lower odds of tolerance to the drug. Furthermore in this group of white non-Hispanic patients, those who tolerated citalopram were more likely to experience remission after the treatment. Serious adverse events such as arrhythmias caused by QT prolongation have been associated with SSRIs, especially citalopram, in poor metabolizers. Other frequently observed complications of this group of drugs include central nervous system effects e.g. headache, insomnia, gastrointestinal and sexual dysfunction. Significantly lower exposure to citalopram, escitalopram and sertraline was found in ultrarapid metabolizers when compared to normal metabolizers. They had an increased probability of failing therapy (Hicks et al. 2015; Spina and de Leon 2016). In studies carried out by Winner et al. (2013), Singh (2015) and Torrellas et al. (2017) patients receiving genotype based individualized antidepressant prescription, had greater response and remission rates in comparison to those treated by the trial-and-error principle.

For the safety and efficacy of administration of some psychiatric drugs it is important to combine CYP genotyping and TDM. Figure 1 summarizes the treatment recommendations for TCAs and SSRIs based on *CYP2C19* phenotype (Hicks et al. 2015, 2017).

In 2017, strategies for personalized medicine implementation in mood disorders were proposed by Amare et al. (2017). The first strategy suggests genetic testing enrollment based on candidate genes (including *CYP2C19*) or gene products before therapy initiation. The second one aims to understand the biological pathways, net- works, and modules underlying drug-response. The third one is based on the development of multivariable diagnostic and prognostic algorithms in order to predict therapeutic outcomes.

CYP2C19 represents a minor deactivating pathway in clozapine metabolism to its active metabolite norclozapine, but Vasudev et al. (2017) identified the role of its polymorphism in the variability of drug pharmacokinetics. PM status was associated with a higher clozapine blood level. Metabolic syndrome was recognized to be significantly correlated with drug concentration and *CYP2C19*2* genotype. This was the first such study in a Caucasian population.

CYP2C19 is also involved in the metabolism of some benzodiazepines, including diazepam and clobazam. Diazepam is a benzodiazepine, primarily metabolized to the major active metabolite, desmethyldiazepam, which is found in the plasma at concentrations equivalent to diazepam. 3-Hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) are minor active metabolites in plasma. In PMs, standard doses of this drug may lead to a higher exposure to diazepam. This is connected with its lower plasma clearance compared to normal metabolizers, and the fact that diazepam had a longer plasma half-life. However, the FDA does not recommend a reduced dose of diazepam in *CYP2C19* poor metabolizers (Dean 2012c). As observed in this group of patients, concentrations of N-desmethylclobazam, clobazam's active metabolite with an antiepileptic potency approximately equivalent to diazepam but less than its parent compound, are higher in *CYP2C19* poor metabolizers than in normal metabolizers. For this reason, according to FDA information, the initial dose in PMs should be 5 mg/day. These patients should be titrated initially to 10-20 mg/day, and may be titrated further to a maximum daily dose of 40 mg if tolerated. In this population of patients, levels of N-desmethylclobazam were 5-fold higher in plasma and 2- to 3-fold higher in urine than in *CYP2C19* normal metabolizers (FDA annotation for clobazam).

Some studies suggest that more attention should be paid in the clinical administration of methadone, used to treat opioid-dependent patients, to individuals carrying *CYP2C19* alleles. However, the results of this research are controversial because methadone is only slightly metabolized by the *CYP2C19* isoenzyme (Mouly et al. 2015). Wang et al. (2013) found that the *CYP2C19* genotype influences R-methadone serum concentrations, and hence dosage adjustments, as well as having the potential to induce cardiac side effects in the form of QTc prolongation in normal metabolizers.

2.4. Impact on antifungal treatment

Antifungal agents, especially azoles, are used not only for the treatment of topic fungal diseases, but also systemic and invasive infections (Moriyama et al. 2017). The drug mostly related to the *CYP2C19* genetic variation is voriconazole (VCZ), a second generation broad-spectrum triazole agent. It is both a substrate and an inhibitor of CYP2C19, the enzyme responsible for conversion of VCZ to inactive metabolite voriconazole-N-oxide. Its use may be limited by adverse reactions such as hepato-, neurotoxicity, visual disturbances, skin rash, erythroderma, nausea, vomiting, diarrhea and cardiovascular events including tachyarrhythmias and QT interval prolongations on electrocardiography. The factors responsible for inter-patient differentiation of VCZ concentrations are *CYP2C19* alleles, age, hepatic function, drug interactions and inflammation. The aforementioned factors and its nonlinear pharmacokinetics indicate that voriconazole is a good candidate for therapeutic drug monitoring (Moriyama et al. 2017; Obeng et al. 2014).

Correlation between poor, normal and ultrarapid metabolizers and voriconazole pharmacokinetic inter-patient variability has been documented. Values of total body clearance were lower and the area under the curve is higher in PMs compared with UMs. Poor metabolizers might be at higher risk of toxicity because of increased trough concentrations, whereas ultrarapid metabolizers might experience underexposure to medication. This therapeutic failure could lead to extension of hospital stay, escalation of therapy and fatal complications. Pre-emptive genotyping of *CYP2C19*, before VCZ loading dose administration might identify at-risk patients, and would enable the clinician to escalate the dose and monitor patients closely (Obeng et al. 2014). Gautier-Veyret et al. (2015) showed the importance of combination analysis of *CYP2C19* and *CYP3A4*22* in patients treated with voriconazole, due to the impact of genetic factors on VCZ C_{min}/D ratio. Furthermore they found that IMs for the *CYP2C19* have a higher C_{min}/D than patients with UM phenotype. Dolton et al. (2014) underline the need for therapeutic drug monitoring (TDM) and CYP2C19 determination during voriconazole treatment in order to establish initial dosing of the drug. Li et al. (2016) showed that patients with PM phenotype are associated with increased treatment success rate, and that there is no correlation between *CYP2C19* polymorphism and daily maintenance dose or adverse events especially hepato- and neurotoxicity. In a new study carried out by You et al. (2018) evidence for age, liver status and *CYP2C19* mutations especially increased enzyme activity dependency on sub-therapeutic voriconazole concentrations was given.

2.5. Impact on oncology

Tamoxifen is an antiestrogenic prodrug, which is widely used in the treatment of estrogen receptor-positive breast cancer. It is bioactivated by enzymes, such as CYP2B6, CYP2C9, CYP2D6, CYP3A4/5 and CYP2C19, which catalyzes the formation of three metabolites, including N-desmethyl-tamoxifen, 4-hydroxy-tamoxifen and 4-hydroxy-N-desmethyl-tamoxifen (endoxifen). The results of studies corresponding with the role of *CYP2C19* genotype in the efficacy of tamoxifen administration

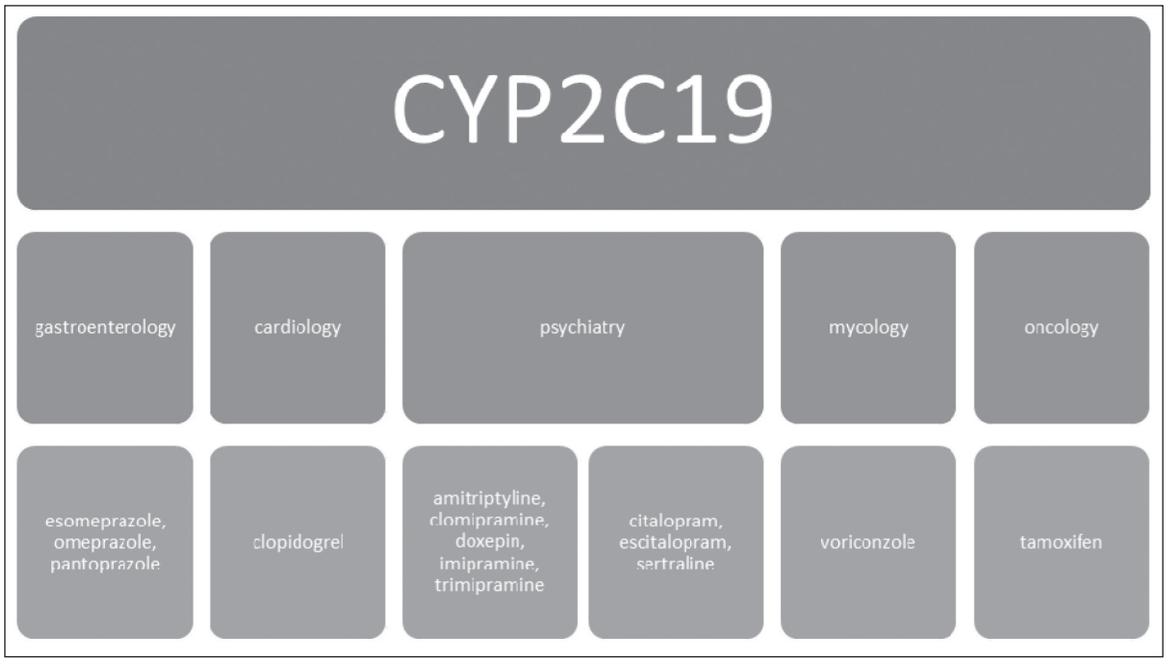

Fig. 2: Drugs which metabolism is influenced by CYP2C19

are controversial (de Vries Schultink et al. 2015). One of them demonstrated that the presence of a *2 allele has been associated with longer relapse-free time or better survival, and the *17 allele with more favorable outcomes in breast cancer patients treated with tamoxifen (Bai et al. 2014). In a study carried out by Beelen et al. (2013) postmenopausal women treated with tamoxifen due to breast cancer who showed variability in *CYP2C19* genotypes experienced different outcomes and advantages of pharmacotherapy. Patients with a minimum of one copy of the *2 allele had a worse overall prognosis but derived greater benefit from tamoxifen treatment. In a study carried out in premenopausal breast cancer women inter-individual variability of tamoxifen metabolism and its influence on clinical outcome was investigated. *CYP2C19* correlated with norendoxifen concentrations but a significant influence on distant relapse-free survival was shown for the *CYP2D6* isoenzyme independently of ethnicity (Saladores et al. 2015). Damkier et al. (2017) found no correlation between *CYP2C19* polymorphisms and response to tamoxifen. The future will show whether *CYP2C19* may potentially serve as a complementary biomarker for the identification of patients who may or may not benefit from tamoxifen treatment.

The influence of *CYP2C19* genetic variation on treatment success was found not only in breast cancer patients. Kattel et al. (2015) showed a moderate influence of the *CYP2C19*1/*2* genotype on the pharmacokinetic properties of nelfinavir and its metabolite M8 among patients with advanced pancreatic cancer, where the drug was used as a radiosensitizer before radiotherapy .

3. Conclusions

The introduction of pharmacogenetic testing into medical practice would be a good way to minimize negative outcomes of therapy and frequency of adverse drug reactions, and to reduce unnecessary medical costs. Furthermore it could help to improve pharmacotherapy by detecting which treatment is most suitable for the individual patient. The *CYP2C19* gene is one of the most interesting because, as shown in our review, knowledge of its polymorphism could positively affect individual treatment and cause better patient outcomes in many cases. A summary of drugs which metabolism depends on *CYPC19* polymorphism is presented in Fig. 2 (Amare et al. 2017; Amin et al. 2017; Bai et al. 2014; Dean 2012a, b, c; Gawronska-Szklarz et al. 2012; Hicks et al. 2015, 2017; Moriyama et al. 2016).

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