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Association of *ABCB1* gene variants, plasma antidepressant concentration, and treatment response: Results from a randomized clinical study

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ABSTRACT

P-glycoprotein, encoded by the *ABCB1* gene, functions as an ATP-driven efflux pump in the blood–brain barrier, extruding its substrates and thereby limiting their passage into the brain. *ABCB1* polymorphisms predicted antidepressant drug response: Minor allele carriers of SNPs rs2032583 and rs2235015 had higher remission rates than major allele homozygotes. The aim of the current study was to evaluate an *ABCB1* genotype-dependent efficacy of a quick dose escalation strategy.

Depressed inpatients (n = 73) treated with antidepressants that are P-glycoprotein substrates were randomly assigned to a standard or high dose condition for 28 days. HAM-D scores, adverse effects and plasma antidepressant concentration were measured weekly and tested among two intronic SNPs rs2032583 and rs2235015. A treatment as usual control sample (n = 128) was retrospectively matched to the study group by gender, age, and diagnosis.

There was a significant interaction of genotype x plasma antidepressant concentration: Minor allele carriers of rs2032583 [$F(1,65) = 7.221$, $p = 0.009$] and rs2235015 [$F(1,65) = 4.939$, $p = 0.030$] whose plasma drug concentration were within recommended range had a greater symptom reduction at study endpoint which exceeded the therapeutic benefit of the treatment as usual group [for rs2032583: $F(1,163) = 4.366$, $p = 0.038$]. Minor allele carriers of rs2032583 with high plasma drug levels had more sleep-related side effects than major allele homozygotes with high plasma drug levels.

The treatment of MDD can be optimized by *ABCB1* genotyping combined with monitoring of plasma drug concentrations: For minor allele carriers of rs2032583 and rs2235015, plasma antidepressant levels should not exceed the recommended range in order to obtain optimal treatment outcome.

1. Introduction

Antidepressants help relieve the symptoms of major depressive disorder (MDD). However, they do not work in every patient and are often accompanied by undesired side effects. An important impediment for their effectiveness is their ability to pass the blood–brain barrier (BBB). The BBB is highly selective and protects the brain tissue against potentially toxic molecules. It is formed of endothelial cell layers connected via tight junctions which selectively restrict the influx of various molecules from plasma into the brain (Uhr et al., 2003). P-glycoprotein (P-gp) is a transmembrane protein located at the luminal membrane of the endothelial cells that form the BBB. This 1280-amino acid transporter encoded by the *ABCB1* gene is located on chromosome 7q21. P-gp belongs to the *ATP binding cassette* (ABC) family of transporter molecules, which require hydrolysis of ATP to actively transport their substrates via extra- and intracellular membranes. A wide range of substances such as cytostatic drugs, anticonvulsants, and antidepressants are substrates of the P-gp (O'Brien et al., 2012). Animal studies have

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shown that many antidepressants are significant substrates of the P-gp. Antidepressants with currently proven substrate properties are amitriptyline oxide, amitriptyline (Uhr et al., 2000, 2007; Grauer and Uhr, 2004), nortriptyline (Uhr et al., 2000, 2007; Grauer and Uhr 2004; Doran et al., 2005; Ejsing et al., 2006), trimipramine (Uhr and Grauer, 2003), escitalopram (Karlsson et al., 2013), citalopram (Uhr and Grauer, 2003; Doran et al., 2005; Uhr et al., 2008; Bundgaard et al., 2012; Karlsson et al., 2013), fluoxetine (Doran et al., 2005; O'Brien et al., 2013), paroxetine (Uhr and Grauer, 2003; Doran et al., 2005), sertraline (evidence from an *in-vitro* study) (Wang et al., 2008), and venlafaxine (Uhr and Grauer, 2003, 2008; Doran et al., 2005; Karlsson et al., 2010, 2011; Bundgaard et al., 2012). The brain penetrance of mirtazapine (Uhr and Grauer, 2003, 2008) and duloxetine (O'Brien et al., 2013) on the other hand does not seem to be regulated by P-gp function.

Uhr and colleagues (Uhr et al., 2008) were the first to show that inpatients with MDD, specific sequence variants of the *ABCB1* gene significantly influenced the treatment success with antidepressants that are substrates of the P-gp, while this was not the case for patients treated with non-substrates. In this study, patients carrying the minor allele of the *ABCB1* single nucleotide polymorphisms (SNPs) rs2032583 (C/T) and rs2235015 (T/G) had significantly higher remission rates when treated with P-gp substrates than non-carriers of the minor allele. Overall, compared to non-carriers, carriers of the minor allele had 7.7 times higher odds to remit when treated with P-gp substrates. In a recent meta-analysis, we compared 16 pharamacogenetic studies focused on the influence of *ABCB1* genotypes and antidepressant treatment outcome and found that carriers of the minor allele of rs2032583 had better treatment results in inpatient samples (Breitenstein et al., 2015). In an effort to explore therapeutic alternatives for the larger group of non-carriers, we recently conducted a retrospective pilot analysis on data stemming from the Munich Antidepressant Response Signature (MARS) study (Breitenstein et al., 2014). An increase of the P-gp substrate dose had the most beneficial effect on this patient group resulting in a shorter hospital stay. With regard to other treatment strategies (e.g., augmentation strategy, switch to a non-substrate) there were no correlations with therapy outcome at the time of discharge. This finding is in line with a study by Singh et al. (Singh et al., 2012) who found that non-carriers of the minor allele of a functional *ABCB1* variant needed higher doses to remit.

The aim of the present prospective randomized clinical study was to determine *ABCB1* genotype dependent dose and plasma drug level recommendations for antidepressant that are P-gp substrates. According to the results of Uhr et al. (2008) and our previously reported explorative study (Breitenstein et al., 2014), we assumed that clinical response to different drug dosages is determined by *ABCB1* genotype. Accordingly we expected that in non-carriers of the minor allele of SNP rs2032583 and rs2235015 (TT homozygous at SNP rs2032583 or GG homozygous at SNP rs2235015, in the following labeled as "non-carriers") an increase of the substrate dose would be more efficacious than a substrate treatment within the normal dose range. In carriers of the minor allele (C carriers of SNP rs2032583 or T carriers of SNP rs2235015, in the following labeled as "carriers"), we expected no additional effect from dose increase. These patients should already benefit from the standard dose. Moreover, we expected the occurrence of central adverse effects to be higher among carriers compared to non-carriers.

2. Materials & methods

2.1. Subjects

103 patients receiving antidepressant treatment for a major, recurrent or bipolar depressive episode as inpatients at the Max Planck Institute of Psychiatry (MPI-P) in Munich were enrolled in the clinical trial. After enrollment, patients were randomized to a standard or high dose group. Fig. 1 provides information on the assessment of the study group. Patients who did not receive the allocated intervention at least until day 21 (D21) were excluded. 73 patients received the ascribed treatment at least until D21 and did not meet any exclusion criteria (intention to treat sample, ITT). The study was authorized by the national competent authority (BfArM, Bonn, Germany) and approved by the local ethics committee of the Ludwig Maximilians University, Munich, Germany (EudraCT No. 2011-003190-29). The trial was registered under NCT02237937 on ClinicalTrials.gov and was carried out in accordance with the principles of Good Clinical Practice and with the latest edition of the Declaration of Helsinki. Patients enrolled in the study gave their written informed consent. For enrollment, patients needed to have a MDD or a bipolar disorder I or II with a current depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV) of moderate to severe intensity (HAM-D at inclusion/Day 0 > 14). Diagnoses were verified by both a senior physician and an experienced psychiatrist. Subjects younger than 18 or older than 80, with acute suicidality, psychotic symptoms, current alcohol or drug dependence/abuse, severe neurological or medical conditions were excluded, as well as subjects incapable of giving informed consent. Pregnant and breastfeeding women or women of reproductive age not using effective contraception were also excluded from participation. Only patients who received a P-gp substrate in a lower dose than the defined standard dose or patients whose treatment was about to be switched to a P-gp substrate were asked to participate. The decision whether a patient was to receive a P-gp-substrate antidepressant was made by the attending psychiatrist independently of the study. Sample characteristics of the two dosage arms and of a treatment as usual (TAU) patient group are listed in Table 1 (ITT) and Table S1 (PP) (supplementary online material). The TAU sample was retrospectively selected from the MARS project (http://www.mars-depression.de) and matched to the study group by gender, age and diagnosis. The MARS project is a naturalistic study designed to identify predictors for antidepressant treatment outcome in affective disorders (Hennings et al., 2009).

2.2. Study design: antidepressant drug conditions

The clinical trial began on study day 0 (D0) defined as the day on which the patient received the standard dose of the respective P-gp substrate antidepressant for the first time. From admission until D0 a mean time range of 13.3 days passed when patients first received the standard dose. For each study medication, the standard dose and high dose are specified in Table 2. On D0 patients were assigned to one of the two study arms according to a randomization plan. The randomization plan was generated using a random generator (programmed in C++). After assignment to the study arms, the substrate dose was either increased (high dose arm) or kept in the range of the standard dose (standard dose arm) for 28 days. *ABCB1* genotypes were blinded until the end of the study. Dose levels in the standard dose arm were based on recommendations according to manufacturers' guidelines (Summary of Product Characteristics, SmPC). In the high dose arm, substrate dose was increased according to a specified escalation plan (Table S2). While dose group was known to the attending doctor, the study personnel was kept blinded. In case of moderate adverse events, dose escalation was halted or reduced if necessary. Patients who were assigned to the high dose arm were excluded from analysis if less than two of the specified dose increases took place within the study period. Plasma drug concentrations were measured weekly. Independent from the actual dose group, patients were allocated to a high or standard