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CYP2D6 Metabolizer Phenotypes in Patients Undergoing ECT After Antidepressant Therapy

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Pharmacogenet Genomics. 2015 Oct;25(10):515-7

ABSTRACT

Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are common mental disorders. According to present guidelines, the effective antidepressant for treatment of MDD and BD for each individual patient is identified through trial and error switching in sequential treatments. A substantial proportion of depressive patients do not benefit from treatment due to ineffectiveness of medication therapy or incurring serious side effects. *CYP2D6* variants are associated with metabolic profile of antidepressant and have been investigated as a determinant contributor in treatment resistant depression (TRD). Hereby, we investigate the accumulation of aberrant *CYP2D6* genotypes and predicted metabolizer phenotypes (UM, IM, and PM) potentially affecting the antidepressants treatment response in depressive patients indicated for electroconvulsive therapy (ECT) compared to patients with single episode of depression.

Method

84 Dutch Caucasian subjects with unipolar or bipolar treatment resistance depression who underwent ECT were genotyped using Amplichip® *CYP450* Genotyping Test for *CYP2D6* and its metabolizer phenotypes. 208 genotyped patients with single episode of unipolar or bipolar depression were used as controls to examine differences in prevalence of *CYP2D6* phenotypes.

Result

The mean age of ECT cases and subjects with single episode of depression was 62 ± 14 [range: 27-87, F/M: 46/29] and 49 ± 19 [range: 15-91, F/M: 91/117], respectively. Prevalence of *CYP2D6* phenotypes (PM, IM, EM and UM) was "5.3%, 38.7%, 56% and 0.0%"for ECT patients, and "6.4%, 51%, 42.6% and 0.0%" for depressive patients. The type of depression and age (*P*=0.018 [OR=0.33] and 0.001 [OR=1.05], but not *CYP2D6* phenotype were associated with the response to treatment.

Conclusion

The frequencies of genotype-predicted-phenotypes, potentially affecting the treatment response (UM, IM and PM), did not show increased frequency in patients who received ECT for continuation of depression treatment as compared to patients with single episode of depression. Preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in treatment resistance depressive patients undergoing ECT. Further large-scale prospective clinical trials are warranted.

INTRODUCTION

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are common mental disorders and amongst the leading causes of disability worldwide. Currently depression is estimated to affect 350 million people [1] and according to the World Health Organization (WHO) MDD is the eleventh highest cause of disability-adjusted life years (DALYs) worldwide. [2]

While options for treatment include psychotherapy, pharmacotherapy and electroconvulsive therapy (ECT), in both moderate and severe MDD, as well as in BD, antidepressant agents are part of the mainstay of treatment in MDD and can be given in the form of single or multiple antidepressants. Patients diagnosed with BD suffer from recurrent depressions and manic episodes. Between episodes, many patients have a low mood characterized as 'sub-threshold depression'. In BD, mood stabilizers e.g. lithium are the first choice of treatment, and in the case of a bipolar depression, antidepressants may be added to the mood stabilizer. Numerous studies in MDD patients show comparable response rates across different classes of antidepressants [3]. Generally, in patients with insufficient response to a certain antidepressant, the drug dosage can be increased, augmenting drugs can be prescribed or a switch to another antidepressant can be made after an adequate (duration and dosage) trial. [4-6] When multiple treatment steps are required, lower acute remission rates and higher relapse rates during the follow-up phase are to be expected [5, 7]. In spite of the availability of multiple pharmacologic classes of medications and their sequenced trials using available guidelines for depression treatment, 50% of patients with major depressive disorder (MDD) fail to achieve complete remission. [8] ECT, as a non-pharmacological intervention, has been shown a favorable option in such cases of treatment resistant unipolar and bipolar depression [9-12] and could be an effective and relatively safe antidepressant treatment. ECT may, particularly, be a life saving treatment in the case of severe depression with psychotic or catatonic features. However, the level of pharmacoresistance that has to be reached until ECT may be applied is not clear. Although ECT is generally only administered after several medication trials have failed due to the invasiveness of the treatment including hospital admission, repetitive narcoses and possible side effects like cognitive disorders, guidelines indicate that ECT is always an option in severe MDD and bipolar depression. [13] Therefore, the indication for ECT is usually a clinical decision, and ECT patients in general reflect the severe range of the depression spectrum. [14]

Treatment related factors, including noncompliance and inadequate antidepressant use (duration and dosage), are determinants of treatment failure. [15] Though therapeutic drug monitoring for antidepressants is commonly available it is not always routinely applied. Any

plasma concentration of antidepressants below or above the therapeutic range may lead to ineffectiveness or side effects respectively, which in turn could result in poor response to treatment or noncompliance, in both MDD and BD. Consequently, adverse effects are common reasons for switching antidepressants, leading to more medication trials and a sense of medication "resistance." Genetic factors are important determinants in the variation of treatment response in depression disorders as well contributing to its etiology, course and prognosis [16]. The enzyme cytochrome P450 2D6 (*CYP2D6*) plays an important role in the pharmacokinetics of many antidepressants. The *CYP2D6* gene is extremely polymorphic, with over 100 alleles known, explaining part of the observed wide range of variability in CYP2D*6* catalytic activity among individuals [15] and consequently prominent contributor to interindividual drug response. [17-20] The *CYP2D6* genotype can be used to predict the phenotype of the enzyme, and four distinct phenotypes with increasing metabolic capacity are distinguished: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultrarapid metabolizer (UM).

An evident relation between the phenotypes of the *CYP2D6* enzyme and the observed blood concentration of several antidepressants exists. [12] Determining an individual's *CYP2D6* phenotype, or metabolic status, will help identify those that are likely to benefit from modifications to pharmacotherapy. [17] This will improve the patient's experience and compliance with medications, which could decrease the number of trials needed to achieve remission and avoiding treatment resistance. Additionally the *CYP2D6* polymorphism may become more important as the use of different medications in patients with multiple comorbidities, particularly in the elders, might increase the risk for drug–drug interactions.

The purpose of our study is to investigate the prevalence of *CYP2D6* phenotypes in depressive patients who were indicated for ECT treatment as a rapid acting treatment and compared to patients with single episode of depression. Accordingly, we hypothesize that there is an accumulation of aberrant *CYP2D6* genotypes and consequent *CYP2D6* metabolizer phenotype(s) in patients undergoing ECT. Furthermore, we would like to investigate if the patients' characteristics such as age and gender might affect of the acquired association of phenotypes with patient who underwent ECT.

METHODS

Study protocol was exempt from obtaining approval by institutional review board of Leiden University Medical Centre due to the retrospective character of the study and the fact that all ECT patients had been routinely genotyped for *CYP2D6* as part of the local ECT protocol.

Patients

84 Dutch Caucasian subjects with unipolar or bipolar depression that received ECT for treatment of depression in the Department of Psychiatry at the Leiden University Medical Centre (LUMC) from July 2009 to June 2014 were included in the study. All the cases had at least one adequate trial of a major class of antidepressant, sensitive to genetic polymorphism of *CYP2D6*, at their current episode of depression and time of ECT trials. In addition, ECT cases had a history of concomitant therapy with several other antidepressants in their current or prior episodes and sequenced treatment trials, which satisfied the current unstandardized criteria for treatment resistant depression (TRD). [15, 21-27] Patients with bipolar disorder were also receiving a mood stabilizer such as lithium. The exclusion criteria were receiving non-*CYP2D6*-dependent antidepressants, not having reliable medical record on the current medication usage or meeting the inclusion criteria for being on adequate dosage/duration of antidepressants. Indications for ECT were failure of response to treatment (mostly due to treatment resistance depression or intolerability of treatment adverse effects) in unipolar and bipolar depressive patients for severe depression with psychotic features. All the medications and medical information of patients were collected from the psychiatric and medical histories available on CS-EZIS, the electronic patient record file system of LUMC comprised of multiple functional modules for clinicians and researchers.

For the control group, depressive patients (unipolar and bipolar) from mental health clinic GGZ Centraal, Amersfoort, the Netherlands were used. Using electronic patient record files from January 2006 to June 2014, 480 patients with a history of depressive episodes were identified and 208 subjects who had a single episode of unipolar or bipolar depression treated with antidepressants and without history of depression recurrence were screened as the control group.

Genotyping, Phenotype and activity score

Amplichip® *CYP450* Genotyping Test (Roche Diagnostic GmBH, D-68298 Mannheim, Germany) approved by the U.S. Food and Drug Administration (FDA) was used to detect the most common variant alleles of the *CYP2D6* gene in the ECT patients. The Amplichip performs genotyping of two Cytochrome P450 genes and provides the predictive phenotype of the associated enzymatic activities, using DNA purified from human blood. The assay distinguishes 29 known polymorphisms in the *CYP2D6* gene, including gene duplication and gene deletion. Detection of these *CYP2D6* polymorphisms results in the identification of 33 unique alleles, including seven *CYP2D6* gene duplication alleles. Control patients were genotyped for CYP2D6 *3, *4, *5, *6, *9, *10, *41 and gene multiplication as described previously. [28] Subjects were classified, according to their expected phenotype, into four groups of poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizers

as follows: patients with two null alleles (**3, *4, *5, *6*) were classified as PM, patients with a null allele in combination with a deficient (**9, *10, *41*) or a functional allele (defined by the absence of any of the determined mutations), or with two deficient alleles were classified as IM, and patients with a gene duplication (xN) in absence of any of the determined mutations were classified as UM. Patients for whom no phenotype could be predicted, due to unknown identity of the allele multiplied, were classified as "unknown". We also used *CYP2D6* activity score system corresponding to each *CYP2D6* metabolizer categorizations. [17]

Adequate antidepressant therapy and treatment response assessment

In patients with unipolar MDD who underwent ECT for their current episode of depression, an antidepressant trial lasting at least 4 weeks at an optimal dose of the prescribed antidepressant (at least as high as the lowest dose defined as effective in the package insert) for the current or the most recent episode of depression was considered as an adequate treatment for inclusion in the study. [22-25] For bipolar depression, similar criteria of treatment-resistance were used with the provision that failure to respond to antidepressant(s) was along with at least one adequate mood stabilizer in the current depressive episode. [29]

Patients' clinical courses (severity of depressive episodes) and response failure to treatment were validated by the Montgomery-Åsberg Depression Rating Scale (MADRS) [30] prior to ECT trials. The cut-off score of more than 10 was considered as treatment ineffectiveness, indicating patients who were not in remission under current antidepressant trial. [13, 31]

Statistical analysis

Data are presented as Mean ± SD [range]. All the calculations were performed using "SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp., USA, IBM Corp. 2010.

A chi-square test of independence was performed to examine the relation between *CYP2D6* phenotypes with patients who indicated for ECT (cases) and patients with single depressive episode (controls). Binary regression, was applied to test if the result of the association of *CYP2D6* phenotypes with patient groups would be affected by the adjustment of variables of age, sex and unipolar vs. bipolar depression.

RESULTS

After exclusion of eight ECT patients due to exclusion criteria, a total of 76 ECT candidate patients meeting the DSM-IV criteria for a unipolar or bipolar depressive episode disorder who met the inclusion criteria were assessed. Patients with bipolar disorder had adequate mood stabilizer for their current depressive episode resulting in ECT trials as well as an

optimal dose and an adequate antidepressant treatment. The mean age of ECT cases and subjects with single episode of depression were 62 ±14) [27-87, F/M: 46/29] and 49 ±19 [15-91, F/M: 91/117], respectively (Table 1).

Table 1. Patients' clinical characteristics and CYP2D6 phenotype distribution and activity score.

Age, Mean (SD) [range]	62 (14)[27-87]	49 (19) [15-91]
Sex (F/M)[a]	46/29	91/117
Unipolar/bipolar depression	64/12	196/12
CYP2D6 activity score		
Range	0-2	0-2
Median	1.5	1
0-0.5 (%)	10	16
1-2 (%)	90	84
CYP2D6 phenotype (%)[b]		
PM	5.33	6.44
IM	38.67	50.99
EM	56	42.57
UM	0	0

[a]F: female, M: male; [b]PM: poor metabolizer, IM: intermediate metabolizer, EM: extensive metabolizer, UM: ultrarapid metabolizer

Prevalence of CYP2D6 phenotypes and activity score

The prevalence of *CYP2D6* phenotypes (PM, IM, EM and UM) was "5.3%, 38.7%, 56% and 0.0%" and "6.4%, 51%, 42.6% and 0.0%"for ECT patients and depressive patients respectively. The relation between patients groups and *CYP2D6* phenotypes (UM excluded due to frequency of 0.0%) were not significant (χ_2 [df=2, N = 282] = 3.99, *P* =0.136). Median of *CYP2D6* activity scores in ECT patients vs. patients with single episode of depression was 1.5 and 1, respectively.

Adjustment of the association of CYP2D6 phenotype for patients' characteristics

A logistic regression analysis was conducted to investigate the association of covariates (type of depression [unipolar vs. bipolar], age, sex, *CYP2D6* phenotype and activity score) with cases that were indicated for the continuation of their treatment using ECT.

A test of the full model against a constant only model was statistically significant, indicating that some covariates included, conditioned on others, were associated with patient groups (chi square= 39.12, *P*<0.001 with *df*=4*).* The Wald criterion demonstrated that the type of depression and age (*P*=0.018 and *P*= 0.001, respectively), but not the *CYP2D6* phenotype (PM/EM, *P*=0.29), were associated with receiving ECT. Sex and activity score neither were significant contributor to the outcome of treatment (*P*=0.57 and *P*=0.174). Odds ratio (OR) values of age and unipolar depression were 1.05, 0.33, respectively (Table 2). After

adjustment for age, gender, and type of depression, *CYP2D6* phenotype IM compared to EM was associated with patients who were treated with ECT (OR=0.53, *P*=0.03).

Table 2. Adjusted frequencies of CYP2D6 phenotypes and activity score by type of depression (unipolar vs. bipolar), age and sex.

Age	1.05	1.03-1.06	25.1	<0.001*
Unipolar/bipolar depression	0.33	0.13-0.83	5.6	0.018*
Sex (M/F)	0.84	0.47-1.5	0.32	0.55
CYP2D6 phenotype				
EM: Reference			5.47	
PM	0.49	0.12-1.7	1.14	0.29
IM	0.53	0.3-0.96	4.33	0.04*
CYP2D6 activity score				
Low (0-0.5)/High (1-2)	0.55	0.21-1.12	1.87	0.17

[a]F: female, M: male; [b]PM: poor metabolizer, IM: intermediate metabolizer, EM: extensive metabolizer)

Table 3. Frequencies of *CYP2D6* alleles and the predicted CYP2D6 phenotypes in patients indicated for ECT due to antidepressant treatment failure.

*4/*4Xn	0	PM	1
*1/*1	2.0	EM	14
*1/*2	2.0	EM	9
*1/*9	1.5	EM	5
*1/*35	1.5	EM	4
*1/*41	1.5	EM	7
*2/*41	1.5	EM	4
*1/*3	1.0	IM	1
*1/*4	1.0	IM	10
*1/*5	1.0	IM	3
*2/*3	1.0	IM	1
*2/*4	1.0	IM	3
*2/*5	1.0	IM	1
*2/*9	1.0	IM	1
*4/*35	1.0	IM	3
*5/*35	1.0	IM	1
*5/*41	1.0	IM	1
*6/*41	1.0	IM	1
*9/*41	1.0	IM	2
*4/*9	0.5	IM	1
*3/*5	0	PM	1
*4/*4	0	PM	2

DISCUSSION

This study investigated the frequency of the recognized *CYP2D6* phenotypes among patients who had single episode of depression or indicated for ECT due to non-response to treatment for unipolar or bipolar depression or adverse effects to antidepressants. Frequency of UM, IM and PM *CYP2D6* phenotypes were not associated with failure of antidepressant treatment response, i.e. patients who underwent ECT for their continuation of treatment. In another study, Haber et al.'s demonstrated that Hungarian patients with difficult-to-treat depression (N=55) did not exhibit an increased frequency of aberrant *CYP2D6* phenotypes [32] compared to the healthy subjects' *CYP2D6* phenotypes. In our study, the observed allele frequency of UM was 0.0% as opposed to the previously reported frequency of 0.01 in Dutch population (prevalence of 4.5%). [33] Prevalence of *CYP2D6* PMs has been estimated to be 5.5%-9% [34-36] in healthy Dutch volunteers. Consistent with these estimations, the prevalence of PMs in ECT patients and patients with single episode of depression were 5.3% and 6.4%, respectively. The frequencies of IMs in both ECT patients and those with single episode disorders of depression were higher than healthy subjects, [36] such that, after adjustment for other factors, the odds of patients with depression eventually treated by ECT was lower, if they had *CYP2D6* IM phenotypes.

Several studies [37] have demonstrated that poor *CYP2D6* metabolizers have a higher incidence of adverse effects when taking *CYP2D6*-dependent antidepressants and more risk of TRD. [38-42] Laika et al [43] reported that intermediate *CYP2D6* metabolizer status on therapeutic outcome in 365 psychiatric in-patients treated with neuroleptics or antidepressants was associated with delay onset of response to treatment and increased length of hospitalization for patients receiving *CYP2D6*-dependent drugs. They also reported that patients with *CYP2D6* IM phenotypes receiving *CYP2D6*-dependent drug doses above the population median had more side effects after 4 weeks than extensive metabolizers. However, an almost equal number of studies did not find significant evidence to support previously mentioned studies on the effect of IMs and PMs over EMs related to occurrence of nonresponse in psychiatric patients treated with antidepressants. [44-48]

Similarly, several studies have reported an association between ultra-rapid *CYP2D6* metabolizer status and diminished response to antidepressants, [41, 49, 50] but no association was shown in a larger retrospective study. [51] Of note, most these studies are in different population witch represent different allele frequencies of *CYP2D6* phenotype. [33] Despite of the equivocal evidences, the current recommendations for standard doses gives consideration for extreme phenotypes of PMs and UMs. It has been suggested that standard drug dose may not result in therapeutic plasma levels for UMs and may increase the risk of an adverse drug reaction and consequent therapeutic failure in PMs. [33, 41, 52-54] Therefore,

it is proposed that lack of response in EMs (and UMs) could be overcome with the dose escalation of antidepressants, while a compound switch might be more promising in PMs to avoid unresponsiveness to treatment or drug adverse effects. [55] As such, prior knowledge of *CYP2D6* metabolizer phenotypes and therapeutic monitoring might reduce the risk of non-responsiveness to the *CYP2D6*-dependent antidepressants [56] and indication of ECT, at least at earlier stages of treatment of depression. Nevertheless, a routine application of *CYP2D6* genotyping prior to treatment is under debate and our study is not conclusive for such recommendation.

This study further sought to identify possible effect of age, gender and type of depression in prediction of response treatment. While some studies have shown a better response to antidepressants (particularly to SSRIs) among women [57, 58], our data is consistent with Parker and et al.'s finding that women did not show a preferential response to SSRI medication [59]. The failure of gender to be associated with the depression recurrence has also been investigated in larger, epidemiological samples and a multicenter trial. [60, 61] Future studies should consider investigation in potential differences of metabolic ratio among *CYP2D6* phenotypes between women and men [35] in response to antidepressants.

The influence of age of onset on outcome in antidepressant trials is controversial [62]. Our data shows that patients who indicated for applying ECT for the treatment of resistant and recurrent depression were older than patients with single episode of depression. In a long-term randomized clinical trial study by Frank et al. [63], no such association was found. However, previous observations showed that both early onset of depression (<40 years old) and late onset (>50 years old) are associated with a higher risk of depression recurrence. These conflicting results might be explained by the fact that late-onset data have been obtained in clinical populations [64, 65], as compared to early onset of depression and higher risk of recurrence in a nonclinical population [66]. Giles and colleagues showed that only age at onset was significant in predicting a recurrent episode. [67] Lewinsohn and colleagues [68] also demonstrated that a *later age of first episode of depression* was associated to faster recurrence.

Additionally, our data suggests that patients with bipolar depression might have higher risk of receiving ECT as treatment for bipolar depression than those with unipolar depression (odds ratio of 3.0). Relevantly, Ghaemi and colleagues [69] studied the outcomes of antidepressant trials for 41 patients with bipolar depression and 37 with unipolar depression matched by age and sex distribution. They found short-term nonresponse was more frequent in bipolar (51.3%) than unipolar (31.6%) depression. Furthermore Forty et al. [70] compared some clinical features of depression including course of recurrences in a large sample of in a large sample of individuals with major depressive disorder (N=593) and bipolar disorder (N=443). They

found the number of depressive episodes was higher in patients with bipolar depression (*P*=0.006).

Considering the controversial results of the previously performed studies in how much of variability in response to treatment and its outcome might be related to other clinical characteristics of patients or how these factors might affect the metabolizing capacity of antipsychotic drugs, further investigation is required to delineate the relative importance of these confounded variables when predicting the response to treatment of depression.

Our results were drawn from a relatively small set of patients included in a retrospective case-control study and consequently should be interpreted with consideration for the limitations of the study and its design. The major issue for this study and similar ones is the sample size. The frequencies of UMs and PMs might be altogether 10-20% of population. Our study was powered to capture a potential medium effect size of 0.2 in at least one of the *CYP2D6* phenotypes (N=282, df=3, effect size=0.2 at α=0.05 and β=0.20); however, it is probable that the effect size of the association of *CYP2D6* phenotypes of poor and ultrarapid metabolizers is small and less than 0.2. Accordingly, a large sample size (N≈1000 for df=2 or 3, effect size of 0.1 at α=0.05 and β=0.20) is required to capture substantial number of these *CYP2D6* phenotypes and their effect size of interest for clinical studies. In addition, most patients had undergone repeated treatment trials with different medications, which might have caused a heterogeneous sample. This will cause more loss of power for such clinical trials with relatively small to medium sample size.

The unipolar and bipolar depressive patients in our study groups (ECT cases and patients with single episode of depression) represent extreme clinical outcomes (phenotypes) of depression regardless of type of depression; i.e. one group who had received several prior treatments and eventually indicated for ECT and the other with only a single episode of depression. It has been recommended that distinction between unipolar and bipolar depression would help in initial and optimal management. [70, 71] However, according to some biological evidences, it has been suggested that it might be more useful to consider conceptualizing bipolar and unipolar depression as the same illness with the presentation of its clinical features in continuum, particularly when it applies to depressive episodes. [30, 72]

In conclusion, no increase in prevalence of genotype-predicted-phenotypes was observed among patients who received ECT for continuation of depression treatment as compared to patients with single episode of depression. Therefore, preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in depressed patients undergoing ECT. Further large-scale prospective clinical trials are warranted.

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