Cytochrome p4502D6 and serotonin transporter polymorphism in patient with bipolar disorder type II

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Abstract – Bipolar disorder can manifest itself for years with recurring depressive episodes before the first manic, hypomanic or mixed episode occurs. The depressive episode of the bipolar disorder thus frequently remains unrecognised and misdiagnosed as a major depressive disorder and therefore gets inadequately treated with antidepressant monotherapy. This paper reports a case of a patient with bipolar disorder type II, who was treated for several years as a major depressive disorder and failed to show a therapeutic response to antidepressants from the group of selective serotonin reuptake inhibitors. The first manic episode occurred in the course of treatment with selective serotonin reuptake inhibitors. Pharmacogenetic analysis has shown that the patient was an ultra-rapid metabolizer of drugs metabolized by cytochrome P450 2D6, and also had a serotonin transporter s/s genotype. Results of the analysis helped in determining the optimal psychopharmacotherapy for manic and depressive episodes of the bipolar disorder. The paper also discusses a possible serotonin transporter genotype impact to the course and the clinical presentation of the disease.

Key words: cytochrome P4502D6, polymorphism, serotonin transporter, bipolar disorder.

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major depressive disorder (MDD), and therefore inadequately treated with antidepressant monotherapy. According to the current psychiatric classification DSM-V, BD is not diagnosed before an occurrence of a manic or hypomanic episode, while ICD-10 describes, besides a manic and hypomanic episode, a mixed episode in BD as well. [5,6] However, a clinician can consider bipolar depression based on clinical characteristic of depressive episodes. Disease onset before the age of 20, recurrent depressive episodes, which cause the person to be ill most of the time, failure to respond to antidepressants, severe psychomotor retardation, hypersomnia, increased appetite, presence of psychotic symptoms or suicidal ideations are frequently present in patients with bipolar depression. [7,8]

Data on prevalence of mood disorders is significantly changing in the last decade. According to past epidemiological data, BD I is responsible for about 2% of prevalence among mood disorders, in the same percentage as BD II. MDD has been diagnosed in 86% of all patients with mood disorders, and non-specific mood disorder in 10% of the patients. Today, we believe that MDD represents 50% of all mood disorders, BD I about 2%, BD II 15%, while 33% of mood disorders belong to a heterogeneous group of disorders from the bipolar spectrum. [9] Accordingly, it is necessary to adjust the pharmacotherapeutic approach and introduce mood stabilizers to the treatment if BD or a disorder from the bipolar spectrum is suspected. Special attention should be paid to symptoms of the depressive episode, and all medical history data on patients with depression should be carefully analyzed for evidence of possible episodes of elevated mood in the past.

Clinical research has shown that the individual therapeutic response to psychotropic drugs considerably varies, from tendency to develop side effects to therapeutic resistance. In the treatment of a depressive episode, about one third of the patients show no therapeutic response after an adequate therapeutic trial. [8] It is a well known fact the therapeutic response can be affected by different factors, such as the age of the patient, liver or kidney dysfunction, diet, smoking or excessive alcohol use. Recent research shows the lack of response to antidepressant treatment is associated with bipolar disorder, [10] and the association of other psychopathological phenomena with the lack of therapeutic response is also being investigated. However, it is believed that the genetic basis is of key importance for the variability of response to antidepressants. [11,12] Pharmacogenetics studies the influence of specific gene polymorphisms, which are responsible for the function of enzymes important in pharmacokinetics and pharmacodynamics.

Biotransformation of most psychotropic drugs in the liver occurs via cytochrome P450 (CYP P450) superfamily, which consists of more than 50 different enzymes. CYP2D6 has an important role in biotransformation of a large number of antidepressants. [13,14] The gene that encodes the CYP2D6 is located at the locus 22q13.1 and is highly polymorphic, resulting in synthesis of enzymes with different activity. Considering the level of activity of the CYP2D6 in the general population we can distinguish poor metabolizers, rapid or normal, and ultra-rapid metabolizers of antidepressants.

With ultra-rapid metabolizers, the use of antidepressants in the usual therapeutic doses does not result in a therapeutic response, because the drugs do not reach therapeutic plasma levels. However, with poor metabolizers the plasma levels of the drug given in the usual therapeutic doses are higher than recommended, and therefore the likelihood of developing side effects is higher, depending on the dose. [15] Ultra-fast metabolizers
account for 3-10% of the Caucasian popu-
lation, with substantial differences in preva-
lence by geographic areas, which makes the
range of prevalence relatively wide. About
7% of Caucasians are poor metabolizers. [16]

Pharmacodynamics of antidepressants,
i.e. the effect of the drug to pathophysiologi-
cal processes in the central nervous system
(CNS), is also to a large extent genetically de-
termined. Polymorphism in genes, which en-
code enzymes involved in the transport of
monoamines in the CNS, results in the dif-
fferences of the therapeutic response to psy-
chotropic drugs. [17] Antidepressants from
the group of SSRIs are serotonin transport-
er (SERT) inhibitors. Gene polymorphism,
which encodes SERT defines three SERT
genotypes. S/s genotype is associated with a
lower number of SERT units in the presyn-
aptic neuron membrane, because of which
the serotonin reuptake remains inefficient.
Persons with l/l or l/s genotypes have a great-
er number of SERT units. The SSRIs therapy
in patients with l/l and l/s genotype can have
a positive effect, while for patients with s/s
genotype, it is inefficient, [18] and for these
patients, an antidepressant with a different
mechanism of action needs to be selected.

Case report

Patient SĆ was born in 1960. Married, fa-
ther of two adult children, employed in his
own construction company. He had no seri-
ous somatic illness and the psychiatric hered-
ity was negative. Medical history: He grew up
in a coherent multien member family, which he
describes as harmonious. Early psychomotor
development was normal. He finished ele-
mentary school, but did not continue his education
due to a poor financial situation of his fam-
ily. Employed at 16 as a construction worker.
Moved to Zagreb at the age of 18 because of
an employment. Married for 27 years, sec-
dary family harmonious. At the age of 40, he
started his own construction company, where
he stayed employed until today.

Complaints in a form of sombreness, apa-
thy and anxiety began in 2004 at the age of
45. By recommendation of a general practi-
tioner, he occasionally took alprazolam in the
dose from 0.25 to 0.50 mg per day. Symptoms
of depression intensified in 2007, after a back
injury at work. He went to see a psychiatrist
a year after that, after being persuaded by
his family. As major symptoms he describes
gloominess, pessimistic view of future, acute
sense of inferiority and guilt, and lack of en-
ergy and interest. He has trouble sleeping, ex-
periences a loss of appetite. He believes that
his business is not going well and he is very
concerned about the future of his family. A se-
vere depressive episode without any psychotic
symptoms was diagnosed.

A sertraline therapy was prescribed in the
dose of 50 mg per day. During the two follow-
up examinations in the period of six weeks in
total, the patient kept saying that he felt equal-
ly miserable, though he had been taking the
medication regularly. The sertraline dose was
increased to 100 mg per day, after which the
patient did not show up for a follow-up ex-
amination.

Anamnesis morbi: At the end of 2010, af-
ter a two year pause, the patient returns for a
psychiatric examination. He says he had been
taking sertraline in the dose of 100 mg per
day for several months, but it did not help
him at all, so in the end, he has stopped tak-
ing the medication. He feels miserable, apa-
thetic and depressive. Mental state is domi-
nated by lowered mood, feeling of guilt, de-
pressive ideas of failure and psychomotor
retardation. A recurrent depressive disorder
was diagnosed, with current episode severe,
but without any psychotic symptoms.
Paroxetine had been administered in the dose of 20 mg, and after four weeks the dose was increased to 40 mg per day because of the lack of therapeutic response to the initial dose.

Three weeks after the increase of the drug dose, the patient developed his first manic episode, with elevated mood, hostility, psychomotor agitation, pressure of speech and grandiosity, and decreased need for sleep. He was urgently admitted at the University Department of Psychiatry in the Clinical Hospital Center Sestre milosrdnice with a diagnosis of BD I. At the beginning of the treatment the patient was treated with valproate in the dose of 1500 mg per day and quetiapine in the dose of 300 mg on the first day, and 600 mg the second day. After three days the psychomotor agitation began to gradually decreased and by the end of the first week of treatment, his sleep was regulated and pressure of speech and hostility decreased. During the next two weeks the grandiosity was gradually disappearing and the patient became more adequate in contact and behaviour. The mental state was completely stabilized during the month of the hospital treatment and the patient was discharged with a recommendation to take valproate in the dose of 1500 mg and quetiapine in the dose of 600 mg per day.

Diagnostic procedure: After admission to the psychiatric ward, standard laboratory tests had been done and the results were within reference values. Brain CT scan was completely normal.

Bearing in mind that the medical history of the patient included a severe depressive episode, and the patient did not respond to the antidepressant from the group of SSRIs, we decided to do CYP2D6 and SERT genotyping.

The results have shown that the patient is an ultra-rapid metabolizer of drugs which are metabolized by CYP2D6. The genotyping showed that the patient had s/s SERT genotype.

Considering the results of the pharmacogenetic analysis, quetiapine was the optimal therapeutic option for this patient, because it is metabolized by CYP3A4 and the antidepressant effect is most likely achieved by its active metabolite norquetiapine, which is an norepinephrine transporter (NET) inhibitor.

Disease course and outcome: Four months after being discharged from the hospital, the patient stopped taking the medicine and soon developed a moderately severe depressive episode without psychotic symptoms. Upon his next visit to the clinic, the clinical presentation was dominated by depressed mood, lack of energy and insomnia, with the presence of polymorphic somatization.

Given the good therapeutic response to quetiapine in the manic episode and the result of the pharmacogenetic analysis, we opted for a monotherapy with quetiapine in the depressive episode. Quetiapine was titrated to a dose of 300 mg per day. After seven days the patient came for a follow-up and claimed that he felt better, was in a brighter mood, had more energy and slept better. Within three weeks, most of the depression symptoms receded and the patient went back to work. He is now in a stable remission, on quetiapine monotherapy in a dose of 300 mg per day.

**Discussion**

Pharmacogenetic analysis showed that the presented patient was an ultra-rapid metabolizer of drugs which are metabolized by CYP2D6. In the depressive phase, the patient was treated with paroxetine which is metabolized exclusively by CYP2D6, which explains the lack of therapeutic response. However, the patient was previously unsuc-
cessfully treated with sertraline, which is only partly metabolized by CYP2D6, and mostly by other cytochromes (CYP2C19, CYP2C9). Therefore, the CYP2D6 genotyping could not give an answer to the lack of therapeutic response to sertraline in this case.

The genotyping showed the patient had s/s SERT genotype. This is the reason the reuptake of serotonin was slow, in a smaller scale and the treatment of depression symptoms with any drug from the group of SSRIs was inefficient. [19]

Treatment of the depressive episode of the bipolar disorder with the presented patient should therefore optimally be done with mood stabilizers – anticonvulsants or atypical antipsychotics, which are neither metabolized by CYP2D6 nor achieve the antidepressant effect by inhibition of the serotonin transporter. Quetiapine was shown to be effective in the clinical studies in the recommended daily doses in the manic phase as well as the depressive phase of the bipolar disorder. [20,21] Given the pharmacological profile, it was proven as an optimal therapeutic solution in the reported case.

The patient’s manic episode has occurred after the increase of the paroxetine dose, without previous remission of the depressive episode.

Several papers researching the association of SERT polymorphism and the occurrence of manic episodes during antidepressant treatment have already been published. The paper by E. Mundo and associates published in 2001 implies the association of s/s SERT genotype and mania induced by antidepressants, i.e. persons with s/s SERT genotype are more likely to develop a manic episode under SSRIs treatment. [22] The papers published later have not confirmed such an association, however, all later research also showed lower odds ratio in comparison with the research by E. Mundo. [12]

The future research is expected to offer a more precise answer to the question about the role of SERT polymorphism in the development of manic episodes in patients on SSRIs therapy. If such an association could be confirmed, pharmacogenetic analysis would have an important role not only in determining the personalized pharmacotherapy, but in psychiatric prevention as well.

In the reported case the first manic episode of the patient occurred at the age of 51. The question arises as to whether the patient would ever develop a manic episode had he not been treated with SSRIs in the depressive phase, or whether a different choice of pharmacotherapy would change the entire course and outcome of the disease. However, it is important to have in mind that the aetiology of BD is still unknown, multifactorial, and it is therefore not yet certain which factor is decisive for the clinical expression of the disease in the end. Treatment of bipolar depression with antidepressants frequently does not result in a satisfactory remission, with a possible risk of developing a manic episode. Genetic variability can modify the therapeutic response on a pharmacokinetic and pharmacodynamic level to a great extent, and result in a lack of therapeutic response. Pharmacogenetic analysis can therefore help with determining the psychopharmacotherapy and in this way, improve the course and the outcome of the disease.

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None

**Conflict of interest**
None to declare
References


Farmakokinetika u bipolarnom poremećaju

Sažetak: Bipolarni poremećaj može se manifestirati godinama rekurentnim epizodama depresije prije prve manične, hipomanične ili liješane epizode. Depresivna epizoda kod bipolarnog poremećaja stoga često ostaje neprepoznata i pogrešno dijagnosticirana kao veliki depresivni poremećaj, pa posljedično i neadekvatno liječena monoterapijom antidepresivima. U ovom radu, izvještavamo u slučaju pacijenta s bipolarnim poremećajem tipa II, koji je liječen nekoliko godina kao veliki depresivni poremećaj i koji nije pokazivao terapijski odgovor na liječenje antidepresivima iz grupe selektivnih inhibitora ponovne resorpcije serotonina. Prva manična epizoda dogodila se tijekom liječenja selektivnim inhibitorima ponovne resorpcije serotonina. Farmakokinetika analiza je pokazala da pacijent pripada u skupinu ljudi koji ultra-brzo metaboliziraju lijekove koji se metaboliziraju preko citokroma P4502D6 i imaju s/s genotip transportera serotonina. Rezultati ove analize pomogli su određivanju optimalne psihofarmakoterapije za manične i depresivne epizode bipolarnog poremećaja. U radu se također raspravlja o mogućem značaju genotipa serotoninskog transportera na tijek i klinički prezentaciju bolesti.

Ključne riječi: citokrom P4502D6, polimorfizam, serotoninski transporter, bipolarni poremećaj