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*Case Report*

# Clinical Case of a 36-Year-Old Man with Treatment-Resistant Paranoid Schizophrenia: Personalized Therapy Selection

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**Abstract:** Schizophrenia is a common and socially significant mental disorder that requires long-term use of antipsychotics (APs). Long-term use of APs increases the risk of developing adverse drug reactions (ADRs) and/or therapeutic resistance in some patients. This may be due to a genetically determined impairment of APs metabolism by cytochrome P450 enzymes and of APs transport across the blood-brain barrier (BBB) and the cell membrane of APs target neurons in the brain. Pharmacogenetic testing (PGx) is a method to identify a group of patients with a high risk of developing AP-induced ADRs. The aim of the case report is to present the experience of using PGx in a 36-year-old patient with treatment-resistant schizophrenia and a medical history of AP-induced ADRs.

**Keywords:** schizophrenia; therapeutic resistance; unwanted reaction; antipsychotics; pharmacogenetic testing.

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## Introduction

Schizophrenia is one of the most serious and socially significant mental disorders, the prevalence of which reaches millions of cases worldwide. For the treatment of mental disorders, including schizophrenia, drugs are usually used - antipsychotics (APs) [1].

Despite the generation of new APs, the problem of AP-induced adverse drug reactions (ADRs) has not been solved yet, and the accumulated experience in targeted prevention of AP-induced ADRs suggests that most of them can be prevented or their consequences can be significantly reduced [2,3].

This problem causes: a decrease in the quality of patients; reducing the adherence of patients with mental disorders to chronic APs therapy; development of pseudo-resistance to APs; disease progression.

The study of the AP-induced ADRs mechanisms is based on the change in their metabolism and transport, which depends on the following risk factors:

- modifiable factors (choice of AP, its dose, dosing regimen, consideration of comorbid conditions, etc.);

- non-modifiable factors (gender, age of patients, genetic predisposition).

The study of genetic predisposition to the development of AP-induced ADRs is based on associative genetic studies and genome-wide studies of single nucleotide variants (SNVs) and polymorphisms of the candidate genes involved in the metabolism, transport, cumulation, excretion of APs and their active metabolites [3-5].

## Objective

The aim of the case report is to present the experience of using pharmacogenetic testing (PGx) in a 36-year-old patient with treatment-resistant schizophrenia and a medical history of AP-induced ADRs.

## Materials and Methods

### 1.1. Procedure

A pharmacogenetic panel was used based on the pharmacogenetic profile of patients with mental disorders (homo- and heterozygous carriers of risk alleles of low-functional and non-functional SNVs of the *CYP1A2*, *CYP2C9*, *CYP3A4*, *CYP2D6*, *CYP2C19*, *ABCB1* genes encoding cytochrome P450 enzymes involved in APs metabolism and the transporter protein P-glycoprotein (P-gp). PGx was carried out using microchips, while the cumulative risk of developing AP-induced ADRs was assessed due to impaired 1<sup>th</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generations APs metabolism by cytochrome P450 enzymes (*CYP1A2*, *CYP2C9*, *CYP3A4*, *CYP2D6*, *CYP2C19*) and APs efflux of 1<sup>th</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generations cross the blood-brain barrier (BBB) and the membrane of neurons using APs transporter proteins P-glycoprotein (P-gp). The features of the genotype and phenotype of patients, information of genetically determined APs metabolism was determined.

Patients were divided into eight phenotypes (slow transporters, intermediate transporters, extensive transporters, ultrarapid transporters, poor metabolizer, intermediate metabolizer, extensive metabolizer, ultrarapid metabolizer) by testing 29 low-functional and non-functional SNVs of *CYP1A2*, *CYP2C9*, *CYP3A4*, *CYP2D6*, *CYP2C19*, *ABCB1* genes. As a result of testing, a list of APs was obtained, divided into four categories: "use as directed" in case of homozygous carriage of fully functional allelic variants of genes in a patient; "use with caution" in case of heterozygous carriage of low-functional allelic variants of genes; "use with increased caution and with more frequent monitoring" in case of homozygous carriage of low-functional allelic variants of genes; "do not use" in case of homozygous carriage of non-functional allelic variants of genes in a patient.

### 1.2. Inclusion and Exclusion Criteria

The following inclusion criteria were used in selecting patients:

- signed voluntary informed consent;
- age over 18 years;
- established diagnosis of schizophrenia (F20.x);
- taking AP for more than 6 months;
- the presence of AP-induced ADRs.

### 1.3. Procedure for Clinical Testing of the Technique

At visit 1, biological material (venous blood) was collected from the patient. Then the genetic analysis of the sample was carried out by PGx. PGx revealed SNVs of the candidate genes (*CYP1A2*, *CYP2C9*, *CYP3A4*, *CYP2D6*, *CYP2C19*, *ABCB1*) and assessed the cumulative risk of AP-induced ADRs.

At visit 2, personalized therapy was recommended.

At visit 3, clinical observation was carried out in dynamics.

### 1.4. Ethical Aspects

The study was performed in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki. The clinical approbation was carried out within the framework of the state order. The participant signed a voluntary informed consent. The patient did not receive any remuneration for participating in the clinical trial. Researchers did not receive any remuneration for conducting clinical trials.

## Results

### 1.5. Anamnesis of the Disease

Patient M., 36 years old, psychopathological heredity is not burdened. Pregnancy, childbirth and early development without features. He did not attend kindergarten, he was brought up at home. Went to school on time. Graduated from 11 classes of secondary school. Then the university, acquired the specialty of an engineer. He was released from military service (flat feet). Engaged in private business.

Since November 2020 he began to feel that he was being followed, and based on clicks on his phone and hints from the TV, he guessed that wiretapping and covert video surveillance were installed behind him, that some people had received incriminating information about him and were trying to blackmail him.

Then he decided that they wanted to take over his money and business. Then he changed his phone to a simpler one, forced his relatives to do the same, tried to understand the true intentions of his pursuers. He noticed the relationship between all the people around him and the events taking place, "it seemed as if someone was controlling them all." He felt that the persecutors knew all his thoughts in advance, because they read his thoughts, in confirmation of these assumptions, they heard certain sounds and words, the so-called. "signs". Felt that the thoughts in his head were someone else's thoughts made and invested. He realized that he was deliberately controlled by some higher powers, tk. lead him to a certain goal. By the type of sudden insight, I realized that I had angered, I lived wrong, I did bad deeds, which angered Life itself, the so-called Universum (Universal deity). Concluded that persecution by some people is a tool to manage it. Under the influence of these experiences, he realized that he was being led to death, made a suicidal attempt.

He was treated in the psychosomatic department, after discharge he periodically took Phenibut, Atarax. I didn't feel any improvement in my condition, I woke up early for about 3-5 o'clock in the morning with a feeling of hopelessness, doom, ideas of guilt, sinfulness, with a feeling that I was to be punished for my sins. In everything that was happening around him, he saw "signs" that guided his life. He constantly thought that he should atone for his guilt, for example, get rid of things from a past life, so he began to throw personal things into the garbage chute, as well as everything that he had previously touched, including a laptop, mobile phone, things and values of his parents, grandmother's gold watch and more, stopped eating, refused food and water. In this condition, he was first hospitalized in "Psychiatric Hospital No. P.P. Kashchenko", was treated with a diagnosis of "Paranoid schizophrenia, observation period less than a year. Depressive-paranoid syndrome" F20.09. Received for 6 weeks combined therapy with vortioxetine 20 mg/day and olanzapine 20 mg/day, without significant positive dynamics.

After 6 weeks, the condition deteriorated sharply: paranoid production became pronounced, I saw signs everywhere, began to commit rude, often brutal acts, threw items of clothing, personal belongings of other patients, wall clocks, players out of the window, trash can, toilet bowl, hit a neighbor in the ward, categorically from eating and taking pills. He explained that his actions are controlled by the Universe. Therapy was changed to haloperidol up to 30 mg/day, received this treatment for 8 weeks. During therapy, he softened, stopped refusing to eat. However, he reported that he felt an irresistible desire to do things that should "appease" the Universe. I saw certain "signs" in the surrounding events, "hinting at this or that danger, indicating to do bad things. In connection with the development of pronounced EPS in the form of flexor muscle rigidity, akathisia, he

received trihexyphenidyl 4 mg/day. Due to the lack of effect of therapy and repeated spontaneous exacerbation of psychoproduktive symptoms, the therapy was changed to quetiapine 800 mg/day, received this therapy for 6 weeks, there was insufficient therapeutic efficacy and an increase in psychoproduktive symptoms, after consultation with a clinical pharmacologist.

### 1.6. Results of Pharmacogenetic Testing

The results of the PGx performed are presented in **Table 1**.

**Table 1.** Results of PGx in a patient with treatment-resistant schizophrenia (clinically significant deviations are shown).

Gene	Protein	Rs	Normal	Result
CYP1A2	CYP1A2 enzyme	rs2069522	CC	TT
CYP2C9	CYP2C9 enzyme	rs1799853	CC	CT
CYP2C19	CYP2C19 enzyme	rs4244285	GG	AG
CYP3A4	CYP3A4 enzyme	rs28371759	TT	CT
CYP2D6	CYP2D6 enzyme	rs3892097	GG	AG

Thus, the patient showed that the functional activity of the CYP1A2 enzyme (responsible for the metabolism of the following APs: asenapine, clozapine, olanzapine, thiothixene, trifluoperazine, chlorpromazine, haloperidol, perphenazine, quetiapine, thioridazine) was significantly reduced. Homozygous carriage of the low-functional allele T of the rs2069522 variant of the CYP1A2 gene encoding the activity of the CYP1A2 enzyme.

The functional activity of the CYP2C9 enzyme (responsible for the metabolism of the following APs: haloperidol, perphenazine, promazine, clozapine, olanzapine) was reduced by 20%. Heterozygous carriage of the low-functional allele T of the rs1799853 variant (C430T) of the CYP2C9 gene encoding the activity of the CYP2C9 enzyme.

The functional activity of the CYP2C19 enzyme (responsible for the metabolism of the following APs: haloperidol, pipotiazine, perphenazine, promazine, thioridazine, quetiapine, clozapine, risperidone) was reduced. Heterozygous carriage of the low-functional allele A of the rs4244285 variant of the CYP2C19 gene encoding the activity of the CYP2C19 enzyme.

Functional activity of the CYP2D6 enzyme (responsible for the metabolism of the following APs: aripiprazole, risperidone, chlorpromazine, fluphenazine, haloperidol, perphenazine, pimozide, thioridazine, alimemazine, promazine, clozapine, zuclopenthixol, trifluoperazine, levomepromazine, flupentixol, pipotiazine, quetiapine, paliperidone,

sertindol, cariprazine) was reduced. Found: Heterozygous carriage of the low-functional allele A of the rs3892097 variant (1846G>A) of the *CYP2D6* gene encoding the activity of the *CYP2D6* enzyme.

The functional activity of the *CYP3A4* enzyme (responsible for the metabolism of the following APs: aripiprazole, cariprazine, lurasidone, pimavanserin, quetiapine, ziprasidone, haloperidol, perphenazine, alimemazine, zuclopenthixol, promazine, clozapine, sertindol, risperidone, paliperidone) was reduced by 20%. Heterozygous carriage of the low-functional allele T of the rs28371759 variant of the *CYP3A4* gene encoding the activity of the *CYP3A4* enzyme.

Thus, the use of PGx to assess the functional activity of cytochrome P450 enzymes made it possible to explain the development of AP-induced ADRs and pseudoresistance to previously used APs in this patient.

The cumulative pharmacogenetic risk of reducing the metabolism of psychotropic drugs, including APs, with the participation of cytochrome P450 enzymes *CYP1A2*, *CYP2C9*, *CYP2D6* in the patient is regarded as high.

Given that the functional activity of five out of the five studied cytochrome P450 enzymes, which provide the metabolism of psychotropic drugs of a wide range of APs, was significantly reduced, the phenotype of this patient was assessed as a "intermediate metabolizer".

### *1.7. Recommendations for the Patient*

We recommended the patient use the following APs with increased caution and more frequent therapeutic drug monitoring: promazine, clozapine, pipotiazine, risperidone, aripiprazole, fluphenazine, pimozide, alimemazine, zuclopenthixol, trifluoperazine, levomepromazine, flupentixol, paliperidone, sertindol, cariprazine, chlorpromazine, promazine, sertindol, cariprazine, lurasidone, ziprasidone. The starting and target dose of these APs should be reduced by an average of 50% compared to the average therapeutic dose (according to the instructions for these drugs).

We advised the patient to do not use the following APs: asenapine, olanzapine, thiorixene, trifluoperazine, chlorpromazine, haloperidol, perphenazine, quetiapine, thioridazine.

Since there are no APs on the Russian market that are not metabolized through the indicated cytochromes, the APs of choice in this patient may be those APs that are metabolized by several cytochromes, such as clozapine, but with increased caution and more frequent therapeutic drug monitoring and reduced doses.

Because of the severity of paranoid experiences, a high suicidal risk due to delusional behavior, clozapine was prescribed with a gradual increase in dose to 400 mg/day, gradually, against the background of treatment, delusional ideas of influence, relationship, guilt, sinfulness became deactivated, became calm in behavior, did not detect delusional behavior, leveled off mood, reduced anxiety and suicidal risk. He became more friendly, sociable, became interested in reading books, willingly communicated with relatives. In general, he himself reported an improvement in well-being.

There was a positive clinical effect after the correction of psychopharmacotherapy in the form of a reduction in hallucinatory-paranoid symptoms and a reduction in the patient's previously AP-induced ADRs.

## **Discussion**

Of great clinical interest is the study of the role of hepatic metabolism of APs, since most of the typical and atypical APs used in real clinical practice have a hepatic or predominantly hepatic metabolism. Hepatic metabolism of APs can be carried out in various ways, including oxidation, glucuronization, N-deamination, etc. Oxidation is the leading

mechanism of hepatic metabolism of most APs used in clinical practice and is carried out with the participation of liver cytochrome P450 isoenzymes.

Cytochrome P450 (cytochrome P450-dependent monooxygenase) is the common name for enzymes of the P450 family, which are part of the class of hemoproteins and belong to type b cytochromes.

In different people, the set of the cytochrome P450 isoenzymes in the endoplasmic reticulum (ER) and on the inner mitochondrial membrane differs due to genetic characteristics. In this regard, the study of genetically determined changes in the expression of the functional activity of CYP family isoenzymes is of great clinical importance in psychiatry and clinical pharmacology [5-7].

In humans, 57 genes and more than 59 pseudogenes encoding CYP isoenzymes have been identified. These isozymes are divided into 18 families and 43 subfamilies. The following enzymes are mainly involved in the metabolism of 1, 2 and 3 generations APs through the oxidation process: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 [5].

Cytochrome P450 enzyme 1A2 (CYP1A2) is a member of the cytochrome P450, is one of the best characterized. It is responsible for the metabolism of commonly drugs belonging to classes such as antidepressants (ADs), APs, mood stabilizers, beta blockers and sedative/hypnotics. Fluvoxamine, amitriptyline, clomipramine, trimipramine, imipramine and doxepin are common antidepressants primarily metabolized by CYP1A2 enzymes. First generation APs such as chlorpromazine, thioridazine, haloperidol, pimozide, stelazine and piperazine are primarily metabolized by CYP1A2 enzyme. Clozapine and Olanzapine are groups of 2<sup>nd</sup> generation antipsychotics primarily metabolized by CYP1A2. Propranolol, warfarin and theophylline are among the common beta blockers which are primarily metabolized by CYP1A2. Drugs that inhibit CYP1A2 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates. Drugs such as ciprofloxacin, fluvoxamine, verapamil, cimetidine, caffeine and isoniazid are inhibitors of CYP1A2 enzyme. Vegetables such as grape fruit juice, cumic and tumeric are inhibitors of the CYP1A2 enzyme which may lead to increase plasma concentration of psychotropics. Inducers of CYP1A2 enzyme such as rifampin, omeperazole, insulin, barbiturates, omeperazole and carbamazepine shorten action of drugs or increase effects of those biotransformed to active agents [8].

Cytochrome P450 enzyme 2C9 (CYP2C9) is an enzyme that in humans is encoded by the *CYP2C9* gene. The CYP2C9 enzyme is expressed in the liver, to a lesser extent in the duodenum, small intestine, stomach, large intestine, and gallbladder. CYP2C9 is an enzyme of cytochrome P450, which plays an important role in the oxidation of both xenobiotics and endogenous compounds. CYP2C9 accounts for about 18% of cytochrome P450 enzymes in liver microsomes. About 100 drugs are metabolized by CYP2C9, including drugs with a narrow therapeutic index, such as warfarin and phenytoin. The CYP2C9 enzyme is involved in metabolism of a wide range of drugs, including APs. The *CYP2C9* gene is highly polymorphic. For CYP2C9 substrates such as warfarin and phenytoin, a decrease in the activity of this enzyme due to genetic polymorphism or drug interaction can lead to toxicity at normal therapeutic doses of drugs, including many APs: haloperidol, perphenazine, promazine, clozapine, olanzapine [9].

Cytochrome P450 enzyme 2C19 (CYP2C19) includes enzymes that catalyze metabolism of xenobiotics, including some proton pump inhibitors and antiepileptic drugs. In humans, it is the *CYP2C19* gene that encodes the CYP2C19 protein. Enzymes in the CYP2C subfamily, including CYP2C19, account for approximately 20% of cytochrome P450 in the adult liver. These proteins are monooxygenases that catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Polymorphism within this gene is associated with variable ability to metabolize drugs. CYP2C19 also possesses epoxide activity: it is one of the principal enzymes responsible for attacking various long-chain polyunsaturated fatty acids at their double bonds to form epoxide products that act as signaling agents. CYP2C19 takes part in metabolism of

the following APs: haloperidol, pipotiazine, perphenazine, promazine, thioridazine, quetiapine, clozapine, risperidone [9].

Cytochrome P450 enzyme 2D6 (CYP2D6) is a member of the cytochrome P450 super family and it plays a primary role in the metabolism of more than 70 substrate medications, belonging to classes such as ADs, APs, mood stabilizers, antiarthmetics, beta blockers antiemetics, opioid and sedative/hypnotics. It is responsible for the metabolism of about 25% of the commonly prescribed drugs. CYP2D6 primarily metabolizes four of the typical APs medications, such as haloperidol, chlorpromazine, thioridazine and perphenazine, and risperidone from 2<sup>nd</sup> generation antipsychotics. Nortriptyline, paroxetine, fluoxetine, venlafaxine and desipramine are antidepressants which are primarily metabolized by CYP2D6. Propranolol, metoprolol, timolol and alperolol are among the common beta blockers which are primarily metabolized by CYP2D6. Drugs which are metabolized by CYP2D6 may inhibit or induce the action of the enzyme. Drugs that inhibit CYP2D6 will predictably increase the plasma concentrations of the medications or decrease in clearance of substrates. Drugs such as bupropion, fluoxetine, paroxetine, norethindrone, citalopram, escitalopram, sertraline, fluvoxamine, nefazodone, venlafaxine, clomipramine, cocaine, quinidine, and ranitidine are inhibitors of CYP2D6 enzyme [10].

Cytochrome P450 enzyme 3A4 (CYP3A4) is an enzyme that in humans is encoded by the *CYP3A4* gene. The CYP3A4 enzyme is expressed predominantly in the liver, duodenum, and small intestine. This is one of the most important enzymes involved in the metabolism of xenobiotics and drugs in the human body. Its purpose is to oxidize small foreign organic molecules such as toxins or drugs so that they can be removed from the body. CYP3A4 is one of a large group of the cytochrome P450 enzymes. This protein is localized in the ER of hepatocytes, and its expression is induced by glucocorticoids and some other drugs. The CYP3A4 enzyme is involved in the metabolism of 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generations APs: aripiprazole, cariprazine, lurasidone, pimavanserin, quetiapine, ziprasidone, haloperidol, perphenazine, alimemazine, zuclopenthixol, promazine, clozapine, sertindol, risperidone, paliperidone [11].

Membrane transport protein (transporter protein) is a membrane protein that is involved in the movement of ions, small molecules and macromolecules, such as another protein, across a biological membrane. Transport proteins are integral transmembrane proteins. They constantly exist inside the cell and cover the membrane through which they carry substances. Transporter proteins can promote the movement of substances using facilitated diffusion or active transport. In the clinical practice of a psychiatrist, knowledge about the role of transporter proteins and changes in their functional activity and expression at the level of cell membranes of neurons and the BBB can help assess the risk of developing ADRs and therapeutic resistance to a wide range of drugs, including APs, mood stabilizers, antidepressants, anticonvulsants, etc [12].

The analysis of fundamental molecular genetic and pharmacogenetic studies showed that 3 transporter proteins play the most important role in AP transport: P-gp or multidrug resistance protein 1 (MDR1); BCRP - "breast cancer resistance protein"; MRP1 is a protein associated with multidrug resistance 1. P-gp is a membrane protein that is an ATP-dependent efflux pump for drugs and other xenobiotics with broad substrate specificity. Performs the function of a carrier of drugs, including AP, through the BBB and the membrane of target neurons for the action of these drugs. This is important to consider if long-term pharmacotherapy of mental disorders is necessary. It may be associated with the development of multiple drug resistance. The involvement of P-gp has been described in the transport of AP of the 1<sup>st</sup> generation (chlorpromazine, amisulpride, trifluoperazine), 2<sup>nd</sup> generation (clozapine, olanzapine, quetiapine, risperidone, paliperidone) and 3<sup>rd</sup> generation (aripiprazole). At the same time, P-gp is involved in the efflux of other drugs that are often prescribed together with AP, including antidepressants and mood stabilizers. P-gp expression in the brain is highest at the level of the frontal, medial and medialbasal cortex, in the hippocampus, tail, and other organs: adrenal glands, liver, gallbladder, small and large intestines, kidneys, ovaries, and fallopian tubes (in women) [13,14].

Thus, the use of PGx to assess genetically determined changes in the functional activity and expression of these cytochrome P450 enzymes in patients with mental disorders is promising and justified. Schizophrenia is a common and socially significant mental disorder that requires long-term use of APs. Long-term use of APs increases the risk of developing ADRs and/or therapeutic resistance in some patients. This may be due to a genetically determined disorder of APs metabolism in the liver and other organs and systems. PGx is a method that allows to identify a group of patients with a high risk of developing AP-induced ADRs. Foreign panels GeneSight Psychotropic test (GeneSight) [15] and Genecept Assay (Genecept) [16] for PGx do not include many significant non-functional variants of the genes encoding enzymes of the CYP family. When using the GeneSight test, analysis is performed on 59 allelic variants of 8 genes - *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP2B6*, *CYP2D6*, *HTR2A* and *SLC6A4*. The attending physician is provided with information already analyzed by the program based on the results of the patient's genotyping. The conclusion contains a list of antipsychotics and antidepressants divided into 3 categories: "use as directed", "use with caution", and "use with increased caution and more frequent monitoring". The Genecept Assay was developed in the USA. The study is carried out on allelic variants in 20 genes, including *5HT2C*, *MC4R*, *DRD2*, *COMT* and genes of the cytochrome P450 system. The conclusion is provided in the form of a detailed table with recommendations for prescribing medicines for a particular patient. Our experience of using PGx to search for low-functional and non-functional SNVs/polymorphisms of five genes (*CYP1A2*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*) encoding enzymes that are centrally involved in APs metabolism demonstrates the importance of this new personalized approach to the choice of APs and its dosing in patients with a pharmacogenetic profile, a poor metabolizer.

## Conclusion

Our experience of the PGx use based on the pharmacogenetic profile of cytochrome P450 enzymes metabolizing APs in patients with mental disorders and the presented clinical case demonstrate the promise of its use in adult patients not only in the case of ADRs development, but also before the start of therapy. This is important for improving the personalized strategy for choosing APs, their dosing regimen, the rate of dose increase, and the possibility of combination with other APs if polytherapy of mental disorders is required.

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