GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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# The role of CYP2D6 in the metabolism of antidepressants

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GSC Biological and Pharmaceutical Sciences, 2024, 27(03), 154–160

Publication history: Received on 04 May 2024; revised on 15 June 2024; accepted on 18 June 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.27.3.0232

## Abstract

The cytochrome P450 2D6 plays an important role in the metabolism of several drugs, including antidepressants, and it also influences their efficacy and adverse effects. Some of the CYP2D6 genetic variants are closely related with a different metabolism way, depending on its type (PM, MI, normal, UM); that impacts mostly reducing the pharmacologic effects of drugs like haloperidol, duloxetine, venlafaxine, nortriptyline, paroxetine and others because their metabolism depends mainly from CYP2D6.

All of these reduced effects can impact negatively in the treatment of depression because they reduce its half-life elimination, and therefore also leads to reduce the acting time and maxim effect, which results in decreased therapeutic effect. Therefore, an alternative to improve the effectiveness of the treatment is to change it for an antidepressant which is not metabolized by CYP2D6.

**Keywords:** CYP2D6; Genetic variant; Antidepressants; Depression; Metabolism; Ultra-rapid

## 1. Introduction

CYP2D6 is an enzyme complex included in the cytochrome p450 family that is involved in the biotransformation and metabolism of approximately 25% of important drugs and substances [1].

A genetic variant refers to the presence of an alternate form of a gene, known as an allele, which occurs at a low frequency in the population (less than 1%), leading to altered structural or functional expression [2]. CYP2D6 gene is one of the most variant of this family, with more than 60 variant allele**s**, which explains its importance in the metabolism of antidepressant drugs [1].

Currently, 4 types of this genetic variant have been recognized based on their metabolic activity: Poor Metabolizer (PM), Intermediate Metabolizer (MI), Normal Metabolizer and Ultra-rapid Metabolizer (UM) [1]. The focus of this article is on the last variant because of its relevance in antidepressant therapy, as it is directly related to its ineffectiveness.

On the other hand, depression is a widespread chronic medical illness that can affect thoughts, mood, and physical health. It is characterized by low mood, lack of energy, sadness, insomnia, and an inability to enjoy life [3]. This mental disorder can result from a complex interaction of social, psychological, biological factors, or adverse life events like unemployment, bereavement, traumatic events, etc. and is one of the most common medical problems in care practice, so common that it affects about 280 million people around the world. In the severe cases of depression, the consequences could be fatal; for this reason, depression is an important illness which deserves special attention around the world [1].

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## 2. Depression

Depression, also known as major depression, major depressive disorder or clinical depression, is a common but serious mental disorder that involves depressed mood or loss of pleasure or interest in activities for long periods of time; it's like feeling sad constantly, interfering with all aspects of life including relationships with family, friends, community and with yourself [4, 5].

### 2.1. Symptoms

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, commonly a person who is suffering from a depressive episode or other type of depressive disorder, may exhibit almost daily at least three of the clinical symptoms that are described in table 1; so it is therefore of great importance to be able to recognize all of these characteristics, and also to pay special attention at its emergence [5].

**Table 1** Clinical characteristics of depression

| Depression signs and symptoms |
|---|
| Feeling sad or anxious often or all the time |
| Not wanting to do activities that used to be fun |
| Feeling irritable, easily frustrated, or restless |
| Having trouble falling asleep or staying asleep |
| Waking up too early or sleeping too much |
| Eating more or less than usual or having no appetite |
| Experiencing aches, pains, headaches, or stomach problems that do not improve with treatment |
| Having trouble concentrating, remembering details, or making decisions |
| Feeling tired, even after sleeping well |
| Feeling guilty, worthless, or helpless |
| Thinking about suicide or hurting yourself |

### 2.2. Risk factors

Depression can happen to anyone, but some people are more susceptible for some risk factors, mainly persons with a family history of suffer from this disease (hereditary factors), but also experiencing traumatic or stressful events (such as physical or sexual abuse, the death of a loved one, financial problems and others), major life changes, medical problems and abuse of harmful substances such as alcohol or other drugs.

Another important risk factor is gender, since according to the World Health Organization, depression is approximately 50% more common among women than among men [6].

In addition, age can have a great influence among people who develop some form of depression, since this condition reaches its peak in elderly (over 7.5% in women between 55 and 74 years of age, and over 5.5% in men) [4]. Depression also occurs in children and teenagers under 15 years of age, but to a lesser degree than in older adults. However, in recent years there has been an increase in the rate of depression in young adults between 17 and 15 years of age.

It is already known that the risk of developing depression not only depends on the age or the gender, but also on some living conditions such as socioeconomic status, marriage status, family, if they live alone or accompanied, its profession, habits, religion, sexual preferences, traumatic events or certain other.

### 2.3. Diagnosis

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, to make a depression diagnosis, the person has to present about five symptoms everyday, almost the whole day, for at least two weeks. One of the most

important symptoms for determining this disorder is the loss of interest or pleasure in almost all the activities, considering that in childs and teenagers show irritability instead of sadness [7].

### 2.4. Treatment

According to the World Health Organization, the first line treatment for mild depression is psychological treatment, because it can teach new mindset, confronting troubles, or maintaining relations. These treatments can include talk therapy with professionals, based on effective psychological treatments such as behavioral activation, cognitive behavioral therapy, interpersonal psychotherapy and problem-solving therapy [4].

For moderate to severe depression the psychological treatments may be accompanied with antidepressants like selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), MAO inhibitors, and other antidepressants. It is worth noting that antidepressants should not be used in children treatment, nor as first line treatment for teenagers.

## 3. CYP2D6

CYP2D6 is a critical pharmacogene involved in the metabolism of approximately 20% of commonly used drugs across a broad spectrum of medical disciplines, including antidepressants. This CYP is also one of the most genetically variable, so its altered function has been associated with both adverse drug reactions and reduced drug efficacy [8].

The categorization of the status of the CYP2D6 metabolizer is based on the evaluation of enzyme activity, which allows the determination of the type of metabolizer according to its genetics. Its forms includes a poor metabolizer (PM), given by dysfunctional alleles from which an enzyme of deficient activity or with dysfunctional rearrangement in its sequence is obtained; intermediate metabolizers (IM) usually have a functional allele and a dysfunctional allele; normal metabolizers have two whole alleles with functional CYP2D6 enzymes; and ultra-rapid metabolizers (UM) that have elevated activity in the CYP2D6 enzyme due to the presence of more than 2 copies of the gene (commonly CYP2D6*2), exhibiting accelerated metabolism activity for drugs (including antidepressants), which may significantly decrease their effect in certain patients [9].

In the human, the CYP2D6 gene is relatively short and it is located on the long arm of chromosome 22 (22q13.2) encoded by nine exons, is translated into CYP2D6 protein that is located in the endoplasmic reticulum, and is also highly expressed in liver, brain, intestinal tissue and lymphoid cells [8].

### 3.1. Diagnosis

The optimal method to describe CYP enzymes activity is phenotyping; this means to prove the correct metabolism of this group of enzymes. This technique shows the most relevant information for clinical practice, because having an enzyme with poor or ultra-rapid activity reflects the combined effects of a combination of different factors, that could be genetics, environmental or endogenous. But also the genotyping is indeed needed, especially in cases when it is relevant to know the degree of affectation of a specific region of the gene. The most popular techniques currently are PCR and RFLP together, that allow a high level of specificity. However, several problems exist, related to cost and those related to the evaluation of admixed populations where there exist potentially large numbers of alleles. Genetic variants play a role in the individual therapy and drug response, which implies its importance of recognizing a variant that could be implied in a specific mental disorder [10].

## 4. Relation between antidepressant therapy drugs and CYP2D6 genetic variants

For the treatment of depression are commonly used tricyclic antidepressants(TCAs), selective serotonin reuptake inhibitors (SSRIs) and other antidepressants. However, around 50% of patients who receive this treatment may present a decrease in pharmacological response, mainly due to environmental, genetic and pathophysiological factors; this would involve adjusting the dose, or a drug that is metabolized by a different pathway [1].

Most antidepressants are metabolized by cytochrome CYP2D6 such that any type of genetic variant can significantly affect their pharmacological response, thus decreasing the therapeutics effects. The drugs that show the most relevant CYP2D6-dependent metabolism are haloperidol, duloxetine, venlafaxine. nortriptyline, paroxetine and others [1].

**Table 2** Drugs dependent of CYP2D6 metabolism

| Antidepressants | Metabolism Scope of CYP2D6 |
|---|---|
| TCA | |
| Amitriptyline | ++ |
| Maprotiline | +++ |
| Clomipramine | ++ |
| Nortriptyline | +++ |
| Imipramine | ++ |
| Dosulepin | - |
| Doxepin | ++ |
| Opipramol | - |
| SSRI | |
| Paroxetine | +++ |
| Fluvoxamine | ++ |
| Fluoxetine | +++ |
| Sertraline | - |
| Citalopram | -/+ |
| Escitalopram | - |
| Other | |
| Mirtazapine | ++ |
| Mianserine | ++ |
| Venlafaxine | ++ |
| Trazodon | - |
| Moclobemide | - |
| Nefazodon | - |

(+ minor metabolism route; ++ partly metabolized by CYP2D6; +++ major metabolism route; - no CYP2D6 metabolism)

### 4.1. Haloperidol

Haloperidol is a typical antipsychotic that acts primarily as a dopamine D2 receptor blocker in the brain. By blocking dopamine, it helps reduce psychotic symptoms such as hallucinations, delusions, and disorganized thinking. This drug undergoes biotransformation in the liver by CYP2D6 mostly [11, 12]. This genetic variant results in a higher plasma concentration of the drug, leading to variations in the therapeutic effect and side effects [10, 13].

### 4.2. Duloxetine

Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a very important class of antidepressant drugs. Duloxetine represents this class of drugs. These drugs have 2 effects, increase the amount of neurotransmitters and intensify dopaminergic transmission in the prefrontal cortex. Duloxetine is mainly metabolized by mitochondrial isoforms of CYP2D6 and CYP1A2. Poor metabolizers present significantly higher concentrations of antidepressant drugs compared to other groups. However, they are more prone to treatment side effects [14].

### 4.3. Venlafaxine

It is a NA and 5-HT reuptake inhibitor, increasing serotonin levels, norepinephrine, and dopamine in the brain. Venlafaxine is metabolized to O-desmethyl-venlafaxine by CYP2D6 [2]. According to several authors, the oral

metabolization of venlafaxine was up to 4 times lower in poor metabolizers, compared to ultra-rapid metabolizers, as well as prolonged elimination half life [15].

### 4.4. Nortriptyline

Inhibits the reuptake of serotonin and norepinephrine by the presynaptic neuronal membrane, thus increasing the concentration of these neurotransmitters in the synaptic cleft. This Drug is metabolized via hydroxylation to 10-hydroxy-nortriptyline, catalyzed by CYP2D6. This is associated with low levels of therapeutic effects, especially for the PM genotype CYP2D6, which has more adverse effects, but occurs more frequently in the UM genotype [16].

### 4.5. Paroxetine

Paroxetine is a selective serotonin reuptake inhibitor (SSRI). It is FDA approved for major depressive disorder (MDD). The mechanism of action increases the concentration of synaptic serotonin. Paroxetine inhibits CYP2D6 and, thus, its own metabolism. The CYP2D6-dependent metabolism is saturable and there are almost no differences between the PM and EM genotypes. There is no clear evidence about the poor metabolizer status on the plasma concentration of paroxetine and the therapeutic effect or adverse effects [16].

### 4.6. Amitriptyline

Amitriptyline is a drug widely used around the world to combat depression, but it is an antidepressant with a narrow range of therapy, and CYP2D6 genetic variants greatly affect its performance.

Amitriptyline belongs to the class of tricyclic antidepressant drugs (TCAs), which intervene by blocking the reuptake of serotonin and norepinephrine, thereby increasing the amount of these neurotransmitters at synaptic terminals [17].

Patients who are receiving this drug and have genetic variation of ultra-rapid metabolization by CYP2D6 have high probability of failing with the therapeutic goal, since the exaggerated increase of this type of drug leads to the production of less active compounds and a reduced plasma concentration of the active drug [18].

## 5. Adjustment of antidepressant dosage or therapy

During antidepressant therapy, dosage plays a very important role in the effectiveness of treatment. Patients associate the success of therapy with the improvement of their mood and the decrease of depression. UR metabolism by CYP2D6 decreases the active dose in the blood even before it can be harnessed to exert its effect. Dose adjustment is still under investigation for psychological and psychiatric illnesses, especially for UR metabolizers, as these may eventually require doses that exceed the toxic dose. A clinical trial in which the dosage therapy was changed in psychiatric patients that were already diagnosed and treated with no results, found no significant difference after dose titration in psychiatric symptoms, quality of life or global functioning [19].

Because of this, currently, instead of adjusting the dose, it is decided to change the treatment to another drug with a different mechanism of action and whose metabolism is not given by CYP2D6, so that a better pharmacological effect can be obtained in the organism and thus improve the effectiveness of the treatment [1].

Some of these options are ketamine, an anesthetic and serotonin reuptake inhibitor, metabolized by CYP3A [20]. Escitalopram, also a serotonin reuptake inhibitor, whose main metabolizer is CYP2C19 [21]. Bupropion, a dopamine and norepinephrine reuptake inhibitor, which may be a good treatment option and also acts as a CYP2D6 inhibitor. And trazodone, a CYP3A4 substrate, serotonin reuptake inhibitor [22].

## 6. Conclusions

CYP2D6 is important in the treatment of depression, as it is responsible for the metabolism of most first-line antidepressants. Its importance lies in the fact that the gene that codes for this enzyme suffers from multiple variations that result in different types of genetic variants. Ultra-rapid metabolizers are of greater importance since they have 2 functional copies of this gene, which gives rise to an extremely high enzyme activity, leading to a low concentration of the drug in the blood that causes a very low therapeutic index. Understanding these genetic variants helps in dose adjustment or drug change for better therapeutic effect and personalized therapy.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed

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