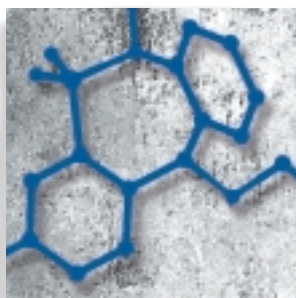


Pharmacogenomics in depression and antidepressants

Brigitta Bondy, MD



Genetic factors are believed to play a major role in the variation of treatment response and the incidence of adverse effects to medication. The aim of pharmacogenetics is to elucidate this variability according to hereditary differences. Considering current hypotheses for the mechanisms of action of antidepressants, most investigations to date have concentrated on mutations in genes coding either for the pathways in the serotonergic and noradrenergic systems or for drug-metabolizing enzymes. Recent studies shifted the emphasis on the main mechanism of drug action from changes in neurotransmitter concentration or receptor function toward long-lasting adaptive processes within the neurons. Although the results are controversial, many studies support the hypothesis that psychopharmacogenetics will help predict an individual's drug response, while minimizing the side effects. The inclusion of functional genomics, which investigates the complex gene and/or protein expression in response to a given drug, may lead to the development of novel and safer drugs.

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Dialogues Clin Neurosci. 2005;7:223-230.

Keywords: pharmacogenetics; pharmacogenomics; antidepressant; serotonin; signal transduction

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The first antidepressants (AD) were discovered by chance almost 50 years ago. Despite recent advances in the discovery and design of ADs, interindividual variability to treatment remains a serious problem in clinical psychiatry. It is well known that there are large differences in dosage requirements and that, with a standard dose of a given drug, a significant proportion of patients do not respond satisfactorily while others suffer from serious adverse effects. In both cases, patients do not benefit from the full therapeutic efficacy and a switch between different treatment regimens is often necessary to find a more suitable alternative.

The variability in drug response is highly complex and can be attributed to several physiological and environmental factors, such as the patient's age, renal and liver function, nutritional status, smoking, alcohol consumption, and physical activity (*Figure 1*). However, it has been recognized for almost 50 years now that genetic factors also influence both the efficacy of a drug and the likelihood of adverse reactions.¹ The concept of pharmacogenetics originated from clinical observations of patients with very high or very low plasma drug concentrations when given a fixed dose, and from the discovery that variations in the DNA sequences of genes coding for metabolizing enzymes are associated with these discrepancies.

The terms *pharmacogenetics* and *pharmacogenomics* are closely related and often used interchangeably. However, the terms do have distinct meanings. Pharmacogenetics represents the variability in drug response and metabolism due to genetic variants, while pharmacogenomics involves the systematic investigation of the human genome and alterations in complex gene and protein expression over time in response to a given drug. There are, however, many interactions between the two

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Selected abbreviations and acronyms

ACE	<i>angiotensin-converting enzyme</i>
AD	<i>antidepressant</i>
BDNF	<i>brain-derived neurotrophic factor</i>
cAMP	<i>cyclic adenosine monophosphate</i>
CYP	<i>cytochrome P-450</i>
HPA	<i>hypothalamo-pituitary-adrenal (axis)</i>
5-HTT	<i>serotonin transporter</i>
PM	<i>poor metabolizer</i>
SNP	<i>single nucleotide polymorphism</i>
SSRI	<i>selective serotonin reuptake inhibitor</i>

approaches and they complement each other at many levels; therefore, the distinction is easily blurred.²

Polymorphisms are investigated in genes coding for either the pharmacokinetic pathways (encompassing the processes that influence bioavailability) or pharmacodynamic pathways (targets of drug action). The majority of studies to date involve single genes or single nucleotide polymorphisms (SNPs), but haplotype analyses of several variants within one or more genes are gaining importance.³ The overall aim of pharmacogenetics is to contribute to drug choice and dosage according to the individual genetic makeup, thus leading to a personalized, more efficacious, and less harmful therapy. This review will give a brief summary of the progress in the field and assess the prospects for future success in this area.

Polymorphic drug-metabolizing enzymes

All ADs are highly lipophilic compounds and, as such, subject to extensive metabolism by a number of enzymes, including those of the cytochrome P-450 (CYP) family. The CYPs were recognized quite as major source of pharmacokinetic variability, as they typically show large interindividual and sometimes intraindividual differences in activities due to genetic variants. More than 50 CYP genes have been described in the human genome to date, but less than 10 of them are of major significance in psychiatry. Among those are CYP 3A, which metabolizes about 50% of all psychotropic drugs, followed by CYP 2D6, CYP 2C19, CYP 1A2, and CYP 2C9.⁴ CYPs show distinct but overlapping substrate specificities; their activities may be induced or inhibited by certain drugs or foodstuffs, such as grapefruit juice (an overview of the major CYPs, their AD substrates, inhibitors, and inducers is given in *Table I*).⁵ Thus, swallowing the drugs with juice or combining them

with other drugs (which is rather common in clinical psychiatry) might have uncontrollable, interactive effects on their bioavailability.⁶

The presence of allelic variants in CYP enzymes with varying degrees of functional significance may result in three main phenotypes, poor metabolizers (PMs), normal metabolizers (NMs), and extensive metabolizers (EMs). The PMs lack an active form of the expressed enzyme due to an inactivating allelic variant; NMs have at least one copy of an active gene; and EMs contain duplicated or amplified gene copies, thus leading to either increased (maybe toxic) or decreased (maybe ineffective) concentrations of the drug.⁷

CYP 2D6 is the most extensively studied P-450 isoenzyme in psychiatry. More than 70 allelic variants have been identified so far, but only a few are clinically relevant, eg, CYP 2D6*3A, CYP 2D6*4B, and CYP 2D6*5, which all lead to the PM phenotype. Moreover, there are considerable ethnic variations in the frequencies of CYP 2D6 mutations, which are more common in Caucasians (7%) and Africans (7% to 8%) than in the Asian population (1%).⁸ In contrast, the incidence of PMs of CYP 2C19 substrates is much higher in Asians (15% to 30%) than in Caucasians.⁵ Several studies have shown a significant contribution of the CYP 2D6 genotype on plasma concentrations of different ADs, and PMs had a higher incidence of side effects.⁹⁻¹¹ Nevertheless, we should keep in mind that the involvement of several different enzymes in the various metabolic pathways may prevent large alterations in in vivo clearance.¹¹ Thus, CYP genotyping can be recommended as a complement to plasma concentration determination when aberrant metabolic capacity is suspected.

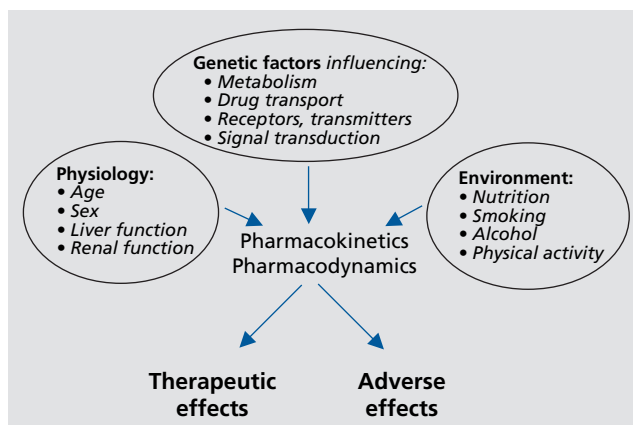


Figure 1. Factors influencing therapeutic drug response.

Pharmacodynamic drug targets

ADs have a wide variety of targets within the neurotransmitter systems, ranging from neurotransmitter synthesis, degrading enzymes, storage, receptors, and specific transport proteins (Figure 2). Variations in DNA sequences of these genes can alter the function or levels of expression of neurotransmitters and enzymes and the binding properties of receptors and transport proteins. Newer concepts address signal transduction proteins and other downstream protein polymorphisms. Most notably, the superfamily of G-proteins, which have a key function in signal transduction and are target proteins for more than 50% of available drugs, is becoming a major goal of investigation. Other downstream proteins, such as the kinases or phosphatases, and proteins downstream to transcription factors, and the expression of proteins are target systems in pharmacogenetics and pharmacogenomics.¹² The proteins, which are related to synaptic and neuronal plasticity have become special goals of interest in terms of drug response.¹³

Pharmacogenetic studies of ADs

According to the pathophysiological mechanisms of affective disorders, which mainly postulate deficiency in monoaminergic neurotransmission, ADs of various classes affect the serotonin, norepinephrine, and dopamine pathways (Table II).

The serotonin transporter (5-HTT) is the initial target of most ADs, especially the widely used selective serotonin reuptake inhibitors (SSRIs). A functional variant was identified in the promoter region of the *5-HTT* gene with an insertion/deletion of 44 bp, resulting in short (*S*) and long (*L*) alleles. The *S* allele reduces the transcriptional

activity of the 5-HTT gene promoter, leading to reduced 5-HTT expression and 5-HT uptake.¹⁴ A number of case-control association studies have outlined that individuals carrying at least one *L* allele, respond more favorably and rapidly to SSRIs, such as fluvoxamine and paroxetine,¹⁵ and the *S/S* genotype had been associated with nonremission in citalopram and fluvoxamine treatment.¹⁵ Taking all the findings together, the emerging picture suggests a marked influence of the *5-HTT* promoter polymorphism on response to SSRIs in Caucasian population.¹⁶ However, opposite findings were reported in the Asian population concerning the frequency of the *L* allele and the response to treatment. The *L* allele frequency in Asians was about one-third that in Caucasians, and persons with the *S/S* genotype responded more favorably to treatment.

These conflicting results are puzzling, but suggest that differential interactions in different populations exist, maybe via interaction with other functional gene variants (for a review, see reference 16). Interestingly, the *5-HTT* variants are not only important for treatment with the SSRIs, but also for those with other compounds, eg, lithium, which is widely used as mood stabilizer. Serretti and colleagues have shown that patients with the *L/L* or *L/S* genotype have a better outcome than those with the *S/S* variant.¹⁷

Current concepts: signal transduction pathways, neuronal plasticity, and stress response

Our present knowledge about the pathophysiological basis of depression and the mechanisms of psychotropic drug action has increased during the last few years. There has therefore been some shift in emphasis from the focus on metabolizing enzymes, neurotransmitter receptors, and

Enzyme	Substrate	Inhibitor	Inducer
CYP 1A2	TCA, fluvoxamine, mirtazapine	Fluvoxamine, grapefruit juice	Carbamazepine, hyperforate, nicotine
CYP 2D6	TCA, SSRIs, mirtazapine, venlafaxine, sertraline	Fluoxetine, fluvoxamine, moclobemide, propranolol	Not known
CYP 2C9	Amitriptyline, fluoxetine, phenytoin	Fluvoxamine	Modafinil
CYP 2C19	TCA, citalopram, moclobemide, venlafaxine, etc	Fluoxetine, valproic acid, fluvoxamine	Modafinil
CYP 3A4	TCA, fluoxetine, mirtazapine, reboxetine, venlafaxine, etc	Fluoxetine, fluvoxamine, grapefruit juice	Hyperforate, modafinil, phenytoin

Table I. Major cytochrome P450 isoenzymes (CYP), their antidepressant (AD) substrates, enzyme inhibitors, and inducers.⁵ TCA, tricyclic AD; SSRI, selective serotonin reuptake inhibitor.

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transporters toward long-lasting adaptive processes, which are related to alterations in signal transduction pathways and mechanisms involving neuronal plasticity, or result from a response to environmental stressors (Figure 2).

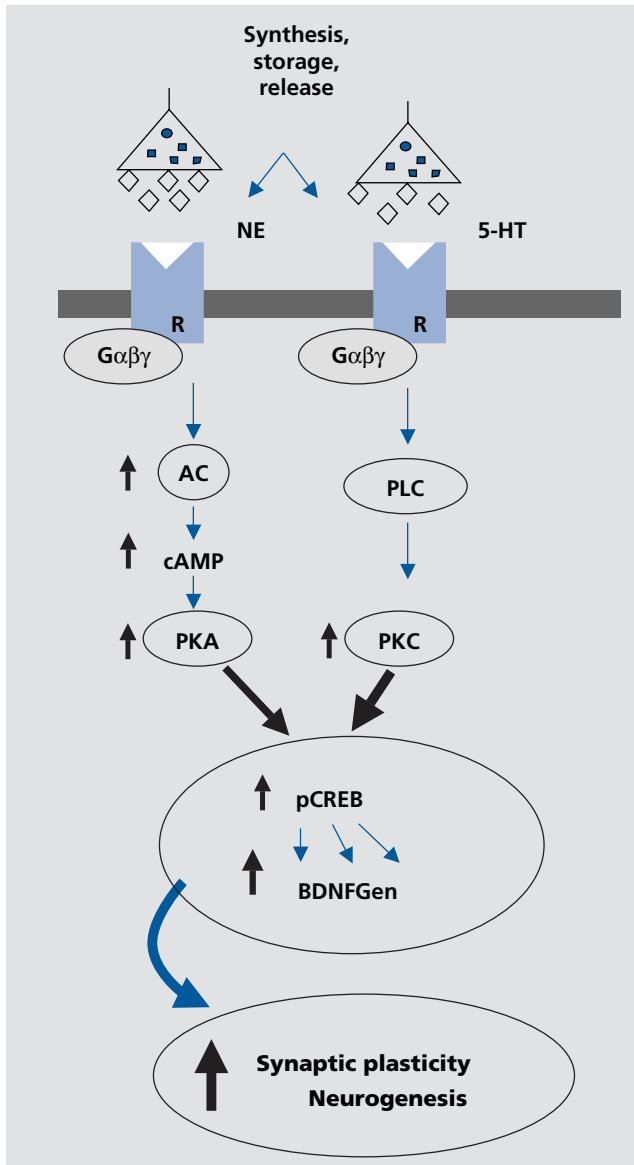


Figure 2. Signal transduction cascade: potential candidate genes for mechanisms of antidepressant action. NE, norepinephrine; 5-HT, 5-hydroxytryptamine (serotonin); R, G-protein-coupled receptor; $G\alpha\beta\gamma$, G-protein- $\alpha\beta\gamma$ complex; AC, adenylylcyclase; PLC, phospholipase C; cAMP, cyclic adenosine monophosphate; PKA/PKC, protein kinase A/C; pCREB, phosphorylated cAMP response element-binding (protein); BDNFGen, brain-derived neurotrophic factor gene.

The majority of studies concerning signal transduction pathways were carried out on polymorphisms within G-proteins, the key elements of intracellular pathway regulation by transmission of signals from receptors to effector proteins. We have investigated a functional polymorphism on the β_3 subunit of the G-protein (C825T), which was shown to increase signal transduction,¹⁸ and found an association of the *T/T* homozygosity to treatment response of ADs.¹⁹ Our results were replicated in two further studies, which showed that patients with the $G\beta_3$ *T/T* variant responded better to AD treatment and that this effect was independent of the analyzed demographic and clinical variables.^{20,21} This finding highlights the possible influence of downstream messenger systems in treatment-mediated responses and may facilitate the identification of novel key targets that may also be relevant in the etiology of depression.

Secondary signaling mechanisms downstream from the receptors and G-proteins, such as cyclic adenosine monophosphate (cAMP), phosphodiesterase, cAMP response element, and cAMP binding proteins are currently under investigation, but only a marginal association has been found so far.²²

In recent years, it has become obvious that chronic treatment with ADs influences the gene expression of potential target genes, eg, neurotrophic factors (brain-derived neurotrophic factor [BDNF]), its receptor (trkB), and vesicle proteins (synapsin I-III, synaptophysin). These proteins are involved in neuronal or synaptic plasticity mechanisms and the transcription factor CREB (cAMP response element binding protein) represents the link between the observed short- and long-term treatment effects (Figure 2).²³ In postmortem studies, an increase of BDNF and trkB levels were found in depressive patients who were receiving AD treatment at the time of death.²⁴ Moreover, the serum levels of BDNF were also decreased in untreated patients and showed a correlation with the severity of symptoms.²⁵ BDNF has not only been associated with affective disorders; it also seems to be essential in mediating the neuroprotective effect of lithium and has been implicated in the mode of action of antipsychotics.²⁶ However, pharmacogenetic studies with polymorphisms in the BDNF gene were thus far inconclusive.

It has been postulated that decreased BDNF seen in depressed patients may be secondary to increased cortisol levels, a phenomenon which has been repeatedly described in alterations of stress-hormone regulation in affective disorders. Hyperactivity of the hypothalamo-pituitary adrenal (HPA) axis with elevated secretion of corticotrophin-releas-

ing factor (CRF), and subsequently cortisol, as well as decreased glucocorticoid receptor sensitivity and disturbed feedback mechanisms are well known.²⁷ In this context, our own results from two independent clinical studies from a cooperation with the Max Planck Institute for Psychiatry in Munich are of importance. To investigate a possible association between genes regulating HPA axis and response to ADs and susceptibility for depression, we genotyped SNPs in genes regulating the HPA axis activity in depressed patients and matched controls. We found significant associations between the response to ADs and SNPs in the *FKBP5* gene, a glucocorticoid receptor (GR)-regulating cochaperone of hsp-90 in two independent samples. Patients homozygous for the minor allele of the associated SNPs responded almost 2 weeks faster to AD drug treatment than patients with the other genotypes.²⁸

Disturbances of the HPA axis are also mirrored by genetic findings in the angiotensin-converting-enzyme (ACE) gene. ACE is not only involved in blood pressure regulation, but is also highly expressed within the central nervous system (CNS), where its primary function comprises degradation of neuropeptides, including bradykinin and substance P. ACE is further supposed to modulate the regulation of the HPA axis, thereby interacting with synthesis and production of neuroactive steroids.²⁹

Within our own studies, we could show that the *D* allele of a functional insertion/deletion (*I/D*) polymorphism (the *D* allele is associated with higher ACE levels and higher neuropeptide degradation capabilities) was associated with several methods of AD treatment, including pharmaco-

logical treatment, electroconvulsive treatment (ECT), transcranial magnetic stimulation (TMS), and sleep deprivation.^{30,31} Moreover, we observed a relationship between the *D* allele and the hyperactivity of the HPA axis, determined by the combined dexamethasone/corticotropin-releasing hormone test.³² Our findings concerning the ACE gene may have a great impact, not only as a missing link between affective disorders and cardiovascular diseases,³³ but also due to a probable function of the ACE gene as a signal transduction component. A recent study has demonstrated that the expression of ACE and other target genes is enhanced by ACE-associated kinases and, therefore, ACE might have an influence on signal transduction mechanisms in the CNS and the periphery.³⁴

Future aspects: from pharmacogenetics to pharmacogenomics

Although the above findings in the field of pharmacogenetics are important, none of the positive results can fully account for the heterogeneity in response to AD treatment. Moreover, due to the complexity of drug response, single mutations in one gene are unlikely to cause the continuous variability in response.

The pharmacogenomic approach uses recent advances in experimental genomics and proteomics (the investigation of all the proteins in a cell or organism), together with the available sequence information of the Human Genome Project. These developments will not only enable genome-wide screens of several millions of SNPs with-

Gene	Polymorphism	Finding
<i>SERT</i>	44 bp ins/del	Response to SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine)
<i>5-HT_{2A}</i>	T102C, C-1420T, G-1438A	No association
<i>TPH1</i>	A218C	C/C associated with better response to fluvoxamine, paroxetine
<i>Gβ₃</i>	C825T	T/T associated with better response
<i>NET</i>	T-182C; G-1287A	No association
<i>MAO-A</i>	30 bp repeat	No association
<i>DRD2</i>	Ser311Cys	No association
<i>DRD3</i>	Ser9Gly	No association
<i>DRD4</i>	48 bp repeats	No association
<i>ACE</i>	ins/del	Discrepant results
<i>BDNF</i>	Val166Met	No association
<i>FKBP5</i>	rs1360780 (C/T)	TT associated with better response

Table II. Pharmacogenetics of antidepressant drugs and candidate genes. *SERT*, serotonin transporter; *5-HT_{2A}*, serotonin receptor 2A; *TPH1*, tryptophan hydroxylase 1; *Gβ₃*, G-protein β_3 subunit; *NET*, norepinephrine transporter; *MAO-A*, monoamine oxidase A; *DRD2*, dopamine D₂ receptor; *DRD3*, D₃ receptor; *DRD4*, dopamine D₄ receptor; *ACE*, angiotensin-converting enzyme; *BDNF*, brain-derived neurotrophic factor; *FKBP5*: FK506 binding protein 5.

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out the use of specific hypotheses and a candidate gene strategy, but also functional investigations of gene and/or protein expression over the whole genome or proteome.³⁵ Although most of the data available so far derived from animal studies, the finding of Landgrebe et al,³⁶ who performed a gene expression analysis in mice treated with paroxetine and mirtazapine, is remarkable. The authors found that both drugs led to a downregulation of four common genes, thus suggesting that ADs with different pharmacological principles of action can share the same molecular targets even through the primary pathways on which they act are different. This finding underlines the recent hypothesis that the initial mechanisms of action trigger subsequent events in the signal transduction cascade and, finally, protein expression.

Although all the above results have to be replicated and validated in further experiments and also analyzed in vivo, there is no doubt that large-scale gene and/or protein expression analysis will be performed in the near future in many laboratories by using all these rapidly growing technologies of functional genomics. The expected results will provide new insights in the pathophysiology of psychiatric disorders. Such detailed knowledge will have profound effects on the diagnosis, prevention, and treatment of these diseases.

Conclusion

Although many investigations have shown that genetic variations in target proteins influence their interaction with ADs, the results are still not conclusive and far from

the original concept of tailoring the drug regimen to an individual's predisposition and predicting a patient's response to therapeutic agents. We have to be aware that the phenotype of drug response is highly complex, representing a classical example of the outcome of gene-gene or gene-environment interactions. Thus, single mutations are unlikely to cause the continuous variability observed in response to psychiatric treatment.

Moreover, clinical factors can be problematic, as they include the confounding variable of placebo response, the issue of inadequate sample sizes, the study of different drug-response phenotypes and patient populations, as well as the use of continual versus categorical outcome measures. Two key elements are needed to perform valid pharmacogenomic studies: explicit and consistent definition of drug-response phenotype and knowledge of polymorphic candidate genes with relevance to the mechanism of drug action. Nevertheless, the field of pharmacogenetics and pharmacogenomics is expanding rapidly, the development of new, fast, and cost-effective methods for the investigation of the individual genetic/genomic profile is under way, and the incorporation of novel research areas, such as pharmacoproteomics, will lead to better insights into disease and treatment processes. The identification of novel drug targets and the determination of patient subpopulations are ambitious methods that may help individualize pharmacological therapy in psychiatry. □

Some of the work reviewed in this article was supported by the German Federal Research Ministry within the promotional emphasis "Competence Nets in Medicine."

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Farmacogenómica de la depresión y los anti-depresivos

Se cree que los factores genéticos juegan un papel principal en la variación de la respuesta terapéutica y en la incidencia de los efectos adversos a la medicación. El objetivo de la farmacogenética es aclarar esta variabilidad de acuerdo con las diferencias hereditarias. Considerando las hipótesis actuales para los mecanismos de acción de los antidepressivos, a la fecha, la mayoría de las investigaciones se han concentrado en las mutaciones de los genes que codifican tanto para las vías de los sistemas serotoninérgico y noradrenérgico como para las enzimas que metabolizan fármacos. El énfasis puesto en el principal mecanismo de acción del fármaco a partir de modificaciones en la concentración del neurotransmisor o en la función del receptor ha sido cambiado en estudios recientes hacia procesos de adaptación a largo plazo dentro de la neurona. Aunque los resultados son controvertidos, muchos estudios sustentan la hipótesis que la psicofarmacogenética ayudará a predecir la respuesta de un individuo al fármaco y a reducir los efectos laterales. La inclusión de la genómica funcional, la cual investiga el complejo gen y/o expresión proteica en respuesta a un fármaco dado, podrá conducir al desarrollo de fármacos nuevos y más seguros.

Pharmacogénomique de la dépression et antidépresseurs

On suppose que les facteurs génétiques jouent un rôle important dans la variation de la réponse au traitement et dans l'incidence des effets indésirables des médicaments. Le but de la pharmacogénétique est d'expliquer cette variabilité d'après des différences héréditaires. Si l'on se réfère aux hypothèses actuelles sur le mécanisme d'action des antidépresseurs, la plupart des recherches à ce jour sont concentrées sur les mutations des gènes codant soit les voies des systèmes sérotoninergiques et noradrénergiques, soit les enzymes intervenant dans le métabolisme des médicaments. Des études récentes sur le principal mécanisme d'action médicamenteuse ont transféré leur intérêt partant des modifications des concentrations en neurotransmetteurs ou de la fonction des récepteurs vers les processus d'adaptation à long terme au sein des neurones. Malgré des résultats controversés, beaucoup d'études sont en faveur de l'hypothèse selon laquelle la pharmacogénétique pourra aider à prévoir une réponse individuelle au médicament tout en réduisant les effets indésirables. L'intervention de la génomique fonctionnelle qui explore le gène complexe et/ou l'expression protéique dans la réponse à un médicament prescrit, peut conduire au développement de nouvelles molécules mieux tolérées.

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