Review

A. Gesteira[1,2,3]
F. Barros[1,2,4]
A. Martín[5,6]
V. Pérez[5,6]
A. Cortés[7]
M. Baiget[7,8]
A. Carracedo[1,2,3,4]

Pharmacogenetic studies on the antipsychotic treatment. Current status and perspectives

[1]Grupo de Medicina Xenómica
Santiago de Compostela
[2]CIBERER U-711
Santiago de Compostela
[3]Universidad de Santiago de Compostela
Instituto de Medicina Legal
[4]Fundación Pública Galega de Medicina Xenómica
[5]Psychiatry Department
Hospital de la Santa Creu i Sant Pau
Barcelona
[6]CIBERSAM
[7]Genetics Service
Hospital de la Santa Creu i Sant Pau
Barcelona
[8]CIBERER
U-705, Barcelona

Based on present knowledge, in this work we review the importance of the pharmacogenetic tests in the treatment with antipsychotic drugs. Many associations have been reported between different genetic markers and response to treatment as well as to the appearance of adverse reactions. However, up to now, no "prime" biomarker capable of unequivocally predicting the clinical benefits of a specific treatment or its toxicity has been identified. The use of individual pharmacogenetic markers has been demonstrated to have little clinical utility, and therefore the combination of information obtained from the analysis of different genes seems to be a more promising strategy. Inclusion of pharmacogenetic tests in clinical trials conducted prospectively and that include a large number of cases could, undoubtedly, significantly contribute to the development of individualized medicine protocols.

Key words:
Pharmacogenetics, Antipsychotics, Cytochromes, Serotonine, Dopamine

Actas Esp Psiquiatr 2010;38(5):301-16

Estudios Farmacogenéticos del tratamiento con Antipsicóticos: Estado actual y perspectivas.

En este trabajo se revisa, a la luz de los conocimientos actuales, la relevancia de los estudios farmacogenéticos en el tratamiento con fármacos antipsicóticos. Se han descrito un gran número de asociaciones entre distintos marcadores genéticos y la respuesta al tratamiento, así como a la aparición de efectos adversos. Sin embargo, no se ha identificado aún ningún biomarcador "estrella" capaz de predecir de forma inequívoca el beneficio clínico de un determinado tratamiento ni su toxicidad. La utilización de marcadores farmacogenéticos individuales se ha demostrado de poca utilidad clínica, por lo que la combinación de la información obtenida del estudio de diversos genes parece una estrategia más prometedora. La inclusión de estudios farmacogenéticos en ensayos clínicos realizados de forma prospectiva incluyendo un elevado número de pacientes podría, sin duda, contribuir de forma significativa al desarrollo de protocolos de medicina personalizada.

Palabras Clave:
Farmacogenética, Antipsicóticos, Citocromos, Serotonina, Dopamina

INTRODUCTION

Schizophrenia is a serious mental disorder included within psychotic disorders. It is calculated that its annual incidence is 0.23 per 1000 persons[1] with a prevalence rate over life of 1%.[2] The precise prevalences in different studies vary from 2.5 to 5.3‰. The annual incidence in Spain has been estimated to be 0.8 new cases per 10,000 inhabitants with the annual prevalence being 3.0‰ in men and 2.86‰ in women.[3] According to the World Health Organization and World Bank, schizophrenia is the 9th most important cause of disability in persons aged 15 to 44 worldwide, and the 4th in developed countries.[4] Furthermore, it accounts for a significant financial expense for society, both because of the treatment cost and public healthcare as well as the indirect costs for family care and losses produced by decreased work productivity and early death, since it is calculated that these patients have a reduced life expectancy of 20% in regards to the general population. This is an increase of 1.6 times the expected mortality and up to 10% died due to suicide.[5-7] We must not overlook the important emotional costs, since this disease causes significant social and psychological exhaustion, both for the patients and their family members.

More than a disease, it is currently considered a syndrome, since different types of schizophrenia are distinguished, depending on the predominant symptoms

Correspondence:
Alejandro Gesteira
Unidad de Medicina Molecular
Hospital Clínico Universitario
C/Choupana s/n 15706 Santiago de Compostela
Tel.: 981.951490 Fax: 981 951473
E-mail: jandrog@gmail.com

(according to the DSM-IV: paranoid, disorganized, catatonic, undifferentiated and residual forms). These symptoms can be divided into 2 groups, that is, positive and negative, both reflecting alterations of the normal functions. The former are due to excess or distortion and the latter to decrease or loss. The positive symptoms can also be divided into 2 dimensions, the "psychotic dimension," which frequently refers to a delusional ideation and hallucinations of any sensory modality, although they are frequently auditory, and the "disorganization dimension," that includes disorganization of both language and behavior. On their part, the negative symptoms suppose restrictions of the setting and intensity of affect, of fluency and productivity of thought, of language and volition. Thus, the diagnoses of this disease is extremely clinical, following defining criteria.[8]

Schizophrenia is generally considered a chronic disorder, although it may follow several patterns, which partially determine the disease prognosis. The course having the best prognosis is that characterized by episodes in which there are positive and/or negative symptoms, which completely abate between episodes. However, residual symptoms that cast a shadow over the prognosis persisted in most of the patients.

One of the factors that undoubtedly affects the disease course is response to drug treatment with antipsychotics. In fact, a meta-analysis of 320 longitudinal studies developed between 1946 and 1967 concluded that introduction of these drugs made it possible to significantly change the course of the patients affected by this disorder, clearly decreasing the number of hospitalizations.[9] We understand antipsychotics to be an extensive and heterogeneous group of drugs having different nature, whose appearance goes back to the beginning of the 1950s. Currently, we can divide them into 2 groups: typical or first generation, and atypical or second-third generation.

Typical antipsychotics are mainly characterized because their therapeutic action is based on the blockade of D2 dopamine receptors in the mesolimbic pathway. However, they also block these receptors in other dopamine pathways, with the consequent side effects due to the decrease of dopamine in these zones, that is, extrapyramidal symptoms due to the increase of acetylcholine in the basal ganglia secondary to the blockade of D2 receptors in the nigrostrial pathway, amenorrhea and other disorders due to the increase of prolactin caused by the blockade in the tuberoinfundibular pathway and the deficit syndrome (negative and cognitive symptoms) due to the blockade in the mesocortical pathway.

Atypical antipsychotics have different action mechanisms. Besides being dopamine antagonists, they may also be antagonists of the serotonergic receptors (such as risperidone, ziprasidone and sertindole), and even of the cholinergics, histaminergics and adrenergics (clozapine, quetiapine and olanzapine). On the other hand, they may specifically block D2 and D3 receptors (amisulpride), or be partial agonists of the dopamine receptors (aripiprazole). They cause fewer extrapyramidal effects then those of the first generation, however they are not exempt from developing equally important adverse reactions, such as, for example, metabolic syndrome, sexual dysfunction, and specifically in the case of clozapine, late-onset agranulocytosis.

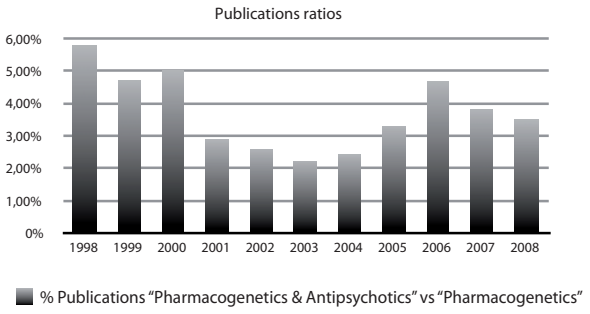

Figure 1 Evolution of the number of publications of Pharmacogenetics of antipsychotics in relationship to the total number of Pharmacogenetic publications. Period 1998-2008

In a recent article,[10] the World Association of Psychiatry reviewed the different studies that compared the effectiveness of the antipsychotics in the treatment of schizophrenia. They reached the conclusion that the atypical ones are as effective as the typical ones in the treatment of positive symptoms,[11] but superior in the treatment of the negative, cognitive and depressive symptoms, with less risk of extrapyramidal effects.[12] In fact, the most representative atypical antipsychotic, clozapine, is the only one that has been demonstrated to be effective in the treatment of antipsychotic-resistant schizophrenia. Therefore, atypical antipsychotics are currently considered as drugs of first line treatment for schizophrenia in the most important clinical guidelines. However, typical antipsychotics are still used frequently, especially in developing countries, given that most of them are patent-free. Another factor that favors their use is their availability in depot form. This allows for intramuscular administration every 2-4 weeks. Thus, it is indicated in those patients with low disease awareness who do not comply with the oral treatment.[13] According to a recent WHO study, the most cost-effective interventions in the developing world are those based on the use of typical antipsychotics together with psychosocial treatment, within a community-based service model. It has been calculated that the relative cost-effective ratio of the interventions based on atypical antipsychotics is much less favorable.[14]

In spite of the advances in the drug treatment for schizophrenia, 40% of the patients with a first episode do not respond favorably to adequate doses of antipsychotics after 6-8 weeks of treatment. Furthermore, the presence of drug-limiting side effects constitute another one of the negative aspects of the current drug alternatives. These, together with lack of psychic disease awareness, favor poor therapeutic compliance, which, in turn, favor relapses - it is estimated that it causes more than 50% of them.[15] These cast a shadow over the patient's prognosis, even leading to absence of response.[16, 17] The factors that influence poor therapeutic compliance are basically appearance of adverse reactions, lack of response, cognitive and memory difficulties presented by these patients and lack of disease awareness, which, in fact, was described at the beginning of the 1970s by Carpenter as the most frequent symptom of this disease.[1821] Along this line, it should be indicated that the multicenter study, CATIE, has described a treatment dropout rate greater than 70% within a period of one year and a half.

Pharmacogenetics is defined by the European Medicines Agency (EMA) as the "study of interindividual variations in DNA sequence related to drug response".[21] These genetic variations may be due to the existence of: i) mutations or polymorphisms that affect one or very few nucleotides. The SNPs (single nucleotide polymorphisms) may be non-synonymous (if they imply a change in any amino acid of the protein or modify promoter activity) or synomymous (if their alteration does not cause amino acid change; ii) VNRT (variable number of tandem repeats) ; iii) events of increase or loss of large genoma regions, which is known as CNVs (Copy Number Variants), as occurs with the CYP2D6 gene. It has been postulated that other factors such as the epigenetics, fundamentally the variation in the methylation patterns, may also be involved in the variability of the drug response.

Since the first CYP2D6 polymorphisms were related with the development of side effects to debrisoquine[22] in 1977, the importance of pharmacogenetics has been increasing. Given that deciding which antipsychotic drug and dose is the best for a given patient is obtained by the trial and error method, the pharmacogenetics of the antipsychotics appeared as one of the most promising fields of study. However, as illustrated in figure 1, in recent years we have been observing a decrease in the number of publications as well as their impact, in favor of other areas such as the treatment of cancer or cardiovascular diseases. There are few cases in which the response behaves as a monogenic trait, and these are, clearly, those more easily translated into clinics.

In the specific field of schizophrenia, candidate gene study approach does not seem to be the best way, considering the probably polygenic and multifactorial etiology of the disease. The same occurs with the response to antipsychotics, since it behaves as a complex polygenic trait and should be understood as a global process, for which both the genes involved in the pharmacokinetics (basically CYPs) as well as in the pharmacodynamics (receptors) are responsible. Even though all of the action mechanisms of the different antipsychotics are not well-known, there is already extensive knowledge on the pharmacogenetics of this type of drug. In the present work, the current data regarding the Pharmacogenetics of the treatment with antipsychotic drugs are reviewed.

GENES INVOLVED IN THE PHARMACOGENETICS VARIABILITY

Cytochrome P450 Genes

Of all the possible enzymes involved in the pharmacokinetics of antipsychotics, Cytochromes P450 or CYPs (a superfamily of low specificity cytochromes involved in Phase 1 metabolism, fundamentally in the liver) have been studied the most, mostly due to their high genetic variability. In many cases, these differences are translated into variability in enzyme activity. In simple terms, Figure 2 shows the importance of the different cytochromes in the metabolism of the drugs.

The enzymes of this protein superfamily, very evolutionarily conserved, catalyze some oxidation reactions of the different substrates to increase their hydrosolubility and to facilitate both their excretion and bioactivation (Figure 3).

In the metabolism of the antipsychotic molecules, the most relevant cytochromes are shown in table 1, and are commented on individually afterwards.

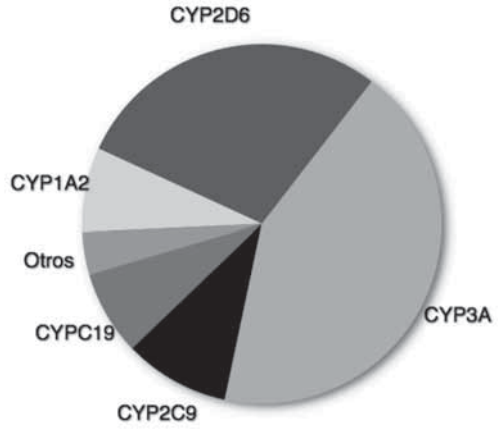

Figure 2 Relative importance of the different CYPs in the metabolism of the medicines

Cytochrome CYP1A2

CYP1A2 accounts for approximately 15% of the CYPs. It is involved in the demethylation of caffeine in the liver microsomes, which may be the most important step in the biotransformation of this molecule, which depends on this enzyme for more than 90% of the activity.[23] Thus, the rate of demethylation of caffeine is used as a method to establish its enzymatic activity (phenotyping).[24] It has been stated that this may be modified by different external factors such as, for example, tobacco: the metabolism of CYP1A2 is significantly increased in smokers due to the action of the polycyclic aromatic hydrocarbons present in tobacco.[25] The influence of external factors on the activity of CYP1A2 is important, since many of its inducers and inhibitors are commonly used substances. As inducers, in addition to tobacco, drugs such as omeprazole, rifampine, ritonavir or carbamazepine must be stressed. As inhibitors, the antidepressants fluoxetine, fluvoxamine,[26] amitriptyline, nortriptyline[27] and caffeine stand out.

CYP1A2 enzyme accounts for approximately 70% of clozapine metabolism, catalyzing the passage of clozapine to N-Demethyl-Clozapine in the liver, so that variations of the CYP1A2 activity has been related to drug clearance.[28] Considering these facts, a role of pharmacogenetic biomarker has been postulated for CYP1A2 in the treatment with clozapine.[28, 29] Olanzapine also mainly uses (in approximately 60%) the CYP1A2 pathway for the formation of its principal metabolites N-demethyl-olanzapine and 7-hydroxy-olanzapine. Thus, it has been shown that variations in CYP1A2 activity affect olanzapine metabolism.[30]

The CYP1A2 gene is located on the long arm of chromosome 15, in region 15q24 and has 7 exons, the first of which is non-coding. The Human Cytochrome P450 (CYP) Allele Nomenclature Committee[31] defines the existence of 16 alleles, numbered from *1 to *16. It also states that 21 subtypes are distinguished in allele *1. Of these alleles, alleles *1C, *1F, *1K, *7 and *11 stand out due to their relationship with the changes in enzyme activity. The presence of alleles *1C, *1K, *7 and *11 is associated to a slow metabolism pattern and it has been postulated that the presence of allele *1F confers a metabolism increase of approximately 1.6 times in smokers.[32] This increase could explain the lack of response to treatment with antipsychotics such as clozapine, and possibly olanzapine, in certain patients. In this regards, several studies have been conducted, but no conclusive results have been obtained.

Cytochrome CYP2D6

Cytochrome CYP2D6 is the first drug-metabolizing enzyme documented as polymorphic.[22, 33, 34] Its involvement in the debrisoquine metabolism is the reason why it is still called debrisoquine-4-hydroxylase. It was with this drug that the first pharmacogenetics implications of CYP2D6 were determined. It participates in the metabolism of opioid analgesics (codeine), antiarrhythmics, beta blockers, many antidepressants (amitriptyline, citalopram, fluoxetine, fluvoxamine, sertraline, etc.)[35, 36] and several antipsychotics (haloperidol, risperidone and aripiprazole).

The CYP2D6 gene is located in the long arm of chromosome 22, in region 22q13 and has nine exons. It is a highly polymorphic gene, and as in other CYPs, there is a nomenclature for its haplotype combinations or alleles. Currently, about 71 alleles have been described,[31] some of which may have up to 13 subtypes, as occurs with CYP2D6*2.

One characteristic of CYP2D6 makes it interesting on the pharmacogenetics level: there is an almost perfect correlation between the enzyme's genotype and metabolitic

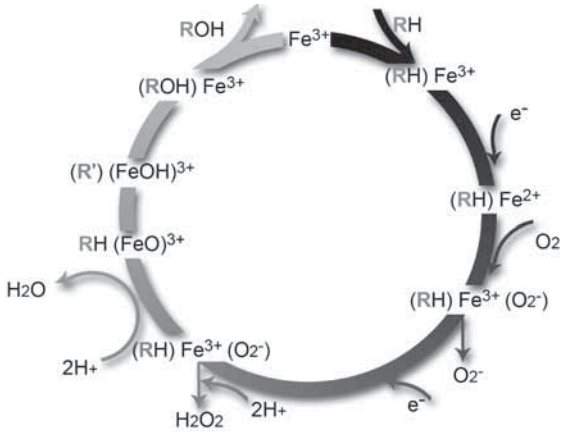

Figure 3 Outline of the monoxidation reaction mediated by the complex cytochrome P450. R is the substrate molecule

Table 1 **Implications of the different CYPs in the metabolism of the most commonly used antipsychotics.**

Antipsychotics	Complex Cytochrome P450 Pathway
Ziprasidone	CYP3A4
Risperidone	CYP2D6
Olanzapine	CYP1A2
Quetiapine	CYP3A4
Haloperidol	CYP3A4, CYP2D6
Clozapine	CYP1A2

Table 2 Frequencies of the most prevalent alleles of CYP2D6 in different ethnic groups

CYP2D6 allele	Enzyme activity	Caucasians (%)[40]	Afro-Americans (%)[42]	Asians (%)[41]	Spanards (%)[43]
*1	functional	30-40	28-50	20-40	31
*2	functional	20-35	10-80	9-20	38
*3	non-functional	1-4	0-0.5	0.8-1	0.9
*4	non-functional	12-13	2-7	0.5-3	13.8
*5	non-functional	1.5-7	0.5-7	4-6	3.3
*6	non-functional	0.5-1	0	-	0.9
*9	reduced	0-3	0	3	2.4
*10	reduced	2-8	3-8	40-70	1.9
*17	reduced	0.1-0.3	10-30	0.5	0
*41	reduced	8	-	-	3.5
*1xN	increased	0.2-1	2-5	0.5	1.9
*2xN	increased	0.5-1.5	1.5-2.5	0-1	1.9
*4xN	non-functional	0.1-0.5	0.9	-	0. 5

activity. Four predictive phenotypes can be differentiated, depending on the combination of the alleles present in an individual.

i) Extensive metabolism:
Those individuals who have 1 to 2 active copies of the gene will have normal metabolism. It is clear that most of the population has this genotype.

ii) Intermediate metabolism:
This may be the most debated class: there are groups that consider Intermediate Metabolizers (IMs) as those individuals having one inactive copy and another with reduced activity, while others reserve this term for those having a single active copy of the gene, (with which the EMs would be those having two active copies). Furthermore, it is believed that this category only has experimental interest, since phenotypically, IMs do not seem to be distinguished from EMs. Thus, both phenotypes are generally grouped when clinically-oriented genotyping is made.

iii) Poor or Deficient metabolism:
Those individuals who have not inherited any active copy of the gene, either because they have two copies of a defective enzyme with decreased activity, or because they only have one copy of the gene (the other copy would be deleted) and this is defective or even because they totally lack the gene (both copies deleted, which is extremely rare), have very slow metabolism related to the normal one and they are called Poor metabolizers (PM).[37] This pattern is that which is most frequently associated with the appearance of adverse effects.

iv) Ultrarapid metabolism:
On the contrary to the previous case, there is the possibility that the individual may have more than two active copies of the gene. Not all the alleles seem to capable of duplication. This has been detected fundamentally in alleles *1, *2, *4, *10 and *35.[38, 39] Of these, only alleles *1, *2 and *35 are active while *10 implies a reduced enzyme activity and *4 encodes a totally inactive enzyme.
An individual with more than 2 copies of a functional allele will express a greater amount of enzyme. This would increase the metabolism of all the substances that use the CYP2D6 pathway. These individuals are called Ultrarapid Metabolizers (UM). Because they may catalyze the drug monooxidation much more effectively, it has much less time to exert its action since it would be rapidly degraded. An UM subject would have a poor therapeutic response at normal doses.

Table 2 shows the frequencies of the most prevalent CYP2D6 alleles in different ethnias.[40-42] The frequencies described in Spanish population are provided.[43]

In addition to the genetic variability, there are external causes capable of modifying the metabolic activity of this gene: several common drugs have CYP2D6 activity inhibitory capacity, such as fluoxetine or paroxetine. Thus, Extensive Metabolizers would behave phenotypically as Poor Metabolizers when there is combined treatment with these drugs, and could develop adverse reactions to treatment that use the CYP2D6 pathway.

CYP2D6 cytochrome is involved in the metabolism of risperidone, in the conversion of risperidone to 9-hydroxy-risperidone. It has been stated that the PMs have high concentrations of the former and low of the latter.

Initially, it was considered that both metabolites were active in the receptor, so that it was believed that neither the metabolizer status of CYP2D6 defined by its allelic variants nor the introduction of inhibitory drugs of this enzyme would affect the effectivity of risperidone. In fact, in the information regarding the drug, it is indicated that no differences have been observed in the appearance of adverse effects between the patients listed as PM or as EM.

Bork et al.,[44] on the contrary, verified the involvement of this gene in the metabolism of this antipsychotic, so that five PM patients of the study developed side effects. In a later study that analyzed 554 patients treated with risperidone, it was demonstrated that PM patients had a 3 times greater risk of developing adverse effects than the EM or IM patients. Furthermore, it was demonstrated that patients with the PM genotype had 6 times more likelihood of dropping out of this treatment than the EMs.[45]

Once demonstrated that reduced or absent activity of the CYP2D6 involves an increase in treatment toxicity, it could be questioned whether the increase of the metabolitic activity in patients with ultra-rapid metabolizer genotype would imply a worse response to treatment. Different studies that have analyzed this subject indicate that this relationship does exist.[46, 47]

Based on current knowledge, the relationship between the UM and UM phenotype does not seem to be bidirectional, that is, although the individuals who have an increase in the number of copies of the CYP2D6 gene have an Ultrarapid Metabolizer phenotype, it has not been observed that there is an increase in the number of copies of the CYP2D6 gene in all the individuals with an Ultrarapid phenotype. Bergmann et al.[48] have demonstrated that the predictive value of the CYP2D6 duplication is low and they suggest that there must be other causes capable of explaining the biological bases of the ultrarapid metabolization beyond the genetic duplications.

In some European and United States healthcare sites, the use of the CYP2D6 genotyping has been proposed as a predictor of response to risperidone.

A relatively recently appearing atypical antipsychotic, that is, aripiprazole, includes the warning in its application guideline that the metabolism of this drug is clearly influenced by the patient's CYP2D6 genotype. However, the need for a pharmacogenetic analysis prior to treatment has not been expressly indicated.

CYP3A cytochrome

The cytochrome P450 3A (CYP3A) family is involved in the metabolism of 45 to 60% of all known drugs (Figure 2). As occurs in other CYPs, this enzyme family has enormous variability in its expression, both in the population and interindividual level.

The most relevant isoforms in the adult in the liver are CYP3A4 and CYP3A5. Both enzymes share substrates and possibly metabolize the same reactions.

The CYP3A4 and CYP3A5 cytochrome genes are located in the long arm of chromosome 7 in the region q21 – q22.1, in a tandem structure. The CYP3A family is responsible for the metabolism of two atypical antipsychotics used in the treatment of psychoses, especially schizophrenia: quetiapine and ziprasidone.[49, 50] It may also act as an alternative enzyme in the metabolism of other drugs such as risperidone.[44]

The CYP3A4 isoform accounts for 30% of all the CYPs presence in the liver and is responsible for the elevated interindividual variability in the metabolism of many drugs that use the CYP3A pathway, which is why it is one of the most studied P450 cytochromes.

It has been estimated that 60 to 90% of the interindividual variability of the CYP3A4 activity in the liver has a genetic basis.[51] However, the allelic frequency studies of this gene and the studies conducted regarding its functionality do not show an equivalent variability. Thus, the existence of other genetic variability mechanisms such as epigenetic phenomena and other still undescribed haplotype variability is postulated.[52] Of the 20 CYP3A4 alleles included in the database "Human Cytochrome P450 Allele Nomenclature," data are available on the enzyme activity of few variants: alleles *8, *11, *13, *16 and *17 are associated to decreased activity. Allele *18A encodes an enzyme whose activity is greater than normal and allele *1 is considered as wildtype associated to a normal activity.[31] The most frequent allele variant is allele *1B characterized by the adenine-to-guanine nucleotide substitution in the position -392. It is estimated that this variant is present in approximately 4% of the Spaniards,[53] however its pharmacokinetic involvement has still not been clarified.

CYP3A4 is the principal responsible enzyme for biotransformation of atypical antipsychotic drugs such as ziprasidone or quetiapine or typical one such as haloperidol. It has been shown that the co-administration of inhibitors (ketoconazole)/inducers (carbamazepine, phenytoin, rifampicine) of CYP3A4 provokes a considerable modification in the action of ziprasidone through the increase or decrease of its liver clearance.[54]

Recently, an association has been described between the presence of the wildtype allele *1A in homozygosis (-392A) and the lack of response to typical antipsychotics such as haloperidol.[55]

Most of the studies performed in Caucasian individuals consider the CYP3A4 isoenzyme as the principal one in the liver because the CYP3A5 expression is low in this population

group (it is present in 33% of the North American Caucasians and in 60% of the Afro-American population).[56] However, it has been demonstrated that that it has as much metabolitic activity as CYP3A4 in individuals in whom CYP3A5 is expressed. Thus, it is believed that it may intervene in the high variability in the response to the CYP3A group mediated drugs.

The Human Cytochrome P450 Allele Nomenclature Committee defines, as occurs with the remaining important CYPs, a series of alleles based on the presence of variations in regards to a wildtype allele or allele *1. The Kuehl et al. experiments[56] indicate that only those individuals who carry allele *1 produce high amounts of total mRNA and express CYP3A5 in their liver, while the two defective alleles described by Kuehl, *3 and *6, would be responsible for the lack of functional CYP3A5. Thus, it has been demonstrated that in CYP3A5*1 allele carriers, CYP3A5 would represent approximately 50% of the total of CYP3A protein. A study conducted in Spanish population shows that the percentage of homozygotes for allele *1 is 2.8%, being the allele frequency 20.2 %.[57] This confers an importance to the CYP3A5 genotype that was previously exclusively reserved for CYP3A4. Recently, it has been associated to the presence of the allele *3 in homozygosis state (6986G) with resistance to typical antipsychotics, especially to haloperidol.[55]

GENES INVOLVED IN PHARMACODYNAMIC VARIABILITY

Serotonin 5-HT2 receptor genes

The importance of the serotonin receptor (5-Hydroxytryptamine, 5HT) 5-HT2A and 5-HT2C, both in the etiology of schizophrenia as well as in its treatment, justifies the study of the genetic variations that could be associated to the disease and to the variability of the antipsychotic response among patients.

Serotonin 5-HT2A receptor gene

This receptor, together with 5-HT2C, belongs to the 5-HT2 receptor group, with proven implications in the effectivity of the second generation antipsychotics. 5-HT2A is a postsynaptic G-protein coupled receptor that has high affinity for clozapine and olanzapine[58] and that could be related with the action of these drugs on the negative symptoms and possibly also on the positive ones. The gene that encodes it, HTR2A, is in the chromosome region 13q14-21, and its most relevant polymorphisms are His452Tyr and 102C>T.

The residue change of histidine to tyrosine in codon 452 is due to a cytosine to thymine nucleotide substitution at position 1354 of the HTR2A gene. This amino acid is located at the C-Terminal cytoplasmatic end of the receptor, in charge of activating the G-protein. The Hazelwood et al. studies have demonstrated that this change does not affect expression nor does prevent the molecules to bind to the receptor, but rather it makes it to be ineffective.[59] This would imply a decrease in efficacy of the antipsychotic molecules, which has been previously verified. Different studies have demonstrated that allele 452Tyr is found more frequently among schizophrenic patients who do not respond to clozapine.[60] Arranz et al. found an association between response and complete genotype (P = 0.07), between response and genotype, considering the allele Tyr452 as recessive (P = 0.02), and between response and the presence of the allele (P = 0.02).[61-63] This association has been verified with a meta-analysis conducted by these authors.[64]

The polymorphism 102C>T deals with, on the contrary, a synonymous change, studied both due to its association with schizophrenia and its role in the response to antipsychotic treatments as clozapine. An association study conducted with 62 patients and 96 controls demonstrated that this polymorphism is more frequently found in schizophrenic patients than in healthy individuals (P = 0.049).[65] This study has been replicated successfully.[66] Regarding the association of this polymorphism with antipsychotic response, it seems that allele 102C is significantly overrepresented among nonresponders compared to responders to clozapine in the European population.[61] Even though other studies[67] have not been able to replicate these results, a meta-analysis of 8 previous studies confirmed the initial results.[64] The relationship of the polymorphism 102C>T to the response to typical antipsychotics has also been demonstrated.[68, 69] On the other hand, the presence of allele C has been related with the appearance of Tardive Dyskinesia (TD) in schizophrenic patients.[70]

As the nucleotide 102 replacement does not produce any change in the amino acid sequence of the receptor, it has been postulated that this SPN has a linkage disequilibrium with some other functional change, either in the coding region, or in the promoter zone. In this sense, the existence of disequilibrium has been detected in regards to a polymorphism of the promoter, -1438A>G. Even though the expression studies of the HTR2A gene with this variation have not offered any conclusive results, the functionality of the promoter region cannot be ruled out as a cause of the association between the silent SNP and the response to antipsychotics. The fact that this linkage disequilibrium is not complete in some populations could explain the discordant data appearing in the literature.

In an association study of the polymorphism in the promoter region, it has been found that the presence in homozygosis of the A allele of this polymorphism is associated to a better response to olanzapine, especially in regards to negative symptoms.[71]

It has been postulated that an epigenetic mechanism could confer functionality to the SNP 102C>T. A recent work[72] has demonstrated that allele C has an allele-specific methylation pattern that modifies the HTR2A gene expression.

Serotonin 5-HT2C receptor gene

The serotonin 5-HT2C receptor is also coupled to G-protein. Both clozapine and olanzapine have high affinity for this receptor. Due to this, the HTR2C gene, located in chromosome Xq24, is an excellent candidate gene for studies on association with the disease and pharmacogenetic ones.

Most of the 5-HT2C receptor gene studies have been focused on a polymorphism located in the coding region, a conversion of guanine to cytosine at position 68, which causes a change of cysteine to serine at codon 23 of the protein, which affects the N-Terminal portion of the receptor, modifying its structure. The 23Ser variant seems to be less common, although population differences have been described between Caucasians and Afro-American descendents.

The first pharmacogenetic studies conducted in a Western European population on this variable and the response to clozapine demonstrated a statistically significant relationship of the 23Ser variant with a better response.[73] In subsequent studies conducted in other European and American populations,[74, 75] the results were not replicated. However, other works[76, 77] have shown a non-significant tendency of association between this allele and good response to clozapine. A meta-analysis conducted after demonstrated this relationship.[78]

Three SNPs (-995G>A, -759C>T and -697G>C) and one VNTR type repeat polymorphism (-1027(GT)) have been described in the HTR2C gene promoter. Certain haplotypes constructed with these polymorphisms have been related with increased promoter activity.[79] Arranz et al. demonstrated that the predictive capacity of the HTR2C gene increases if the repeat polymorphism of the promoter -1027(GT) is added to the Cys23Ser genotype.[77]

A study in Spanish patients that included the polyphorphism –330-GT/-244-CT has demonstrated a tendency to association with response to olanzapine (Mata-Pastor et al., 2002).

Studies aimed at associating the genetic variants of HTR2C with the side effects derived from antipsychotic treatment, fundamentally Tardive Dyskinesia and weight gain, have provided promising, although not very conclusive, results.[80-84]

Serotonin transporter genes

Although serotonin reception is mediated by many pre- and post-synaptic receptors, serotonin recovery on the presynaptic level depends on a single molecule: the 5HTT transporter (5-Hydroxytryptamine Transporter). This is a high affinity, active transporter which, through re-uptake, modulates the extracellular activity of serotonin, taking responsibility for maintaining the presynaptic reservoir of this neurotransmitter.

The gene encoding this transporter is located at the 17q11.1-q12 region. Two principal polymorphisms have been described. These, although they do not affect the transporter protein structure, would modify the gene transcriptional activity.

The repeat polymorphism called 5HTTLPR (5HTT gene-linked polymorphic region) consists in a 44 base pair deletion/insertion in the promoter region, which would involve repeat elements, giving rise to two alleles, one long (L) and one short (S).

The other polymorphism described is a tandem repeat polymorphism, called 5HTTVNTR, located at intron 2 of the 5HTT gene. The most frequent alleles correspond to 9, 10 and 12 repeats.

5HTTLPR has been related with response to clozapine in European population,[77] however the results in Asian population have not been conclusive.[85]

A recent study conducted in 129 Asiatic patients determine the role of both polymorphisms as genetic markers of response to risperidone. However, individually, only 5HTTLPR was predictive. The analyses of haplotypes determined that the presence of L/12 was associated to a good response to this antipsychotic.[86]

Histamine receptor genes

The relationship between the histamine system and schizophrenia[87] has renewed the interest for the study of this system in the pharmacogenetics of the treatment with antipsychotics.

Histamine receptors are, as are the serotoninergic ones, G-protein coupled receptors, through which their function is mediated. There are four types of histamine receptors, that is, H1, H2, H3 and H4. The H2 has been studied the most from the pharmacogenetic point of view. This receptor is expressed in the neurons of most of the cerebral cortex. It has been verified that several tricyclic antidepressants and some antipsychotics have a potent inhibition of the adenylate cyclase-coupled H2

receptors. This implies that this receptor could mediate in the response to this type of drugs. It has also been described that clozapine has high affinity for this receptor.[58]

The gene that encodifies for this receptor (H2) is located at 5q21-23. According to a study published by Arranz et al., the analysis of a group of polymorphisms of the serotonin receptors and transporters (5-HT2A 102T>C, His452Tyr, 5-HT2C -330 GT/-244 CT, 5-HT2C Cys23Ser and 5–HTTLPR) in combination with the polymorphism -1028G>A of the histamine H2 receptor achieves a 76.86% prediction level of response to clozapine.[77]

In a later study, it was only possible to repeat the result in reference to the polymorphism of this receptor, by means of a statistically significant association of allele -1028A with a good response to treatment with clozapine.[88]

Dopamine receptors

Given that antipsychotic drugs, especially the typical ones, are characterized by their antagonistic capacity of the dopamine system, an important role in the etiology of the psychotic disease is attributed to it.

The genes studied the most in relationship with antipsychotic response are those of the D2 and D3 receptors. Studies on the coding genes of other receptors, such as D4, with a high affinity for clozapine, have not been successful.[89-92]

The D2 receptor gene

The blockade of the D2 dopamine receptors seems to be the main action mechanism of the neuroleptics on the positive symptoms of schizophrenia and it is supposed that this same antagonism is responsible for the Parkinsonian-like side effects associated to this type of treatment. Different iresearcher groups have analyzed the validity of different polymorphisms of the DRD2 gene, located in the chromosome region 11q23, as pharmacogenetic markers of response to treatment with antipsychotics.

Polymorphism -141C ins/del seems to be related with D2 receptor expression, so that the presence of the allele -141C del is associated with a greater expression of it.[93] More recently, it has been seen that the carriers of this allele have greater response times in the first treatments with olanzapine and risperidone.[94] Another polymorphism related with D2 expression is the restriction polymorphism known as Taq1A. A1 Allele is associated with lower density of the receptor and decreased function.[95] In a pharmacogenetic analysis,[96] the presence of a diplotype of the Taq1A and -141C ins/del polymorphisms (Ins A2/Del A1) has been related with good response to risperidone. Another polymorphism shown to be predictive of response to this drug is Ser311Cys[97] of the DRD2 gene.

In a recent work,[94] a new polymorphism, A241G, has also been associated with the response to risperidone and to olanzapine, so that allele G carriers would have lower response time. In a study in an Asian population, it was seen that the A allele of this polymorphism is associated with good response to risperidone.[98]

In two recent meta-analyses,[99, 100] it was concluded that there is a relationship between the A1 allele of the restrictions polymorphism Taq1A of the D2 dopamine receptor gene (DRD2) and the appearance of treatment-derived tardive dyskinesia.

The D3 receptor gene

The pharmacogenetics studies including the D3 receptor gene analysis are justified because of the elevated affinity that different typical antipsychotics have for this receptor. The DRD3 gen is located in the chromosome region 3q13.3 and the most studied polymorphism is Gly9Ser.

The presence of the Gly allele in homozygosis has been associated to better response to antipsychotics, especially in regards to positive symptoms.[101, 102] Recently, an association has been found between the T/A/G/A/C haplotype of the rs6280, rs963468, rs2134655, rs1486012 and rs7631540 polymorphisms of the DRD3 gene and lack of response to typical antipsychotics, being the C/G/G/T/T haplotype the most frequent among responders. Furthermore, the presence of this haplotype seems to increase the risk of resistance to neuroleptics associated to those individuals with the *3 allele of the CYP3A5 gene in homozygosis.[55]

In regards to the appearance of side effects, it seems that there is an association between the presence of the Gly allele and tardive dyskinesia.[100, 103-105] The presence of this allele has also been related with the appearance of acute akathisia associated with antipsychiotic treatment.[106]

OTHERS GENES RELATED WITH THE VARIABILITY OF THE ANTIPSYCHIOTIC TREATMENT

The ABCB1 gene

The P-glycoprotein, encoded by the ABCB1 gene, also known as MDR1 (Multidrug Resistance Gene), is a transport molecule expressed in the capillary endothelial cells that cover the blood-brain barrier, regulating the entry of substances from the blood system into the central nervous system. Antipsychotics are included among these substances since high affinity between this transporter and risperidone,

quetiapine or olanzapine has been detected *in vitro*.[107] The MDR1 gene, located at the 7q21.1 region of the genoma, is a very polymorphic gene and in recent studies, different genetic variables of it have been related to the response to antipsychotics. In Asian population, the T/T allele of the 1236C>T polymorphism (rs1128503) has been associated to good response to risperidone.[108] The T allele of the 2677G/T/A polymorphism (rs2032582) has also been associated to good response to Olanzapine in women.[109]

The COMT gene

The COMT gene, located in chromosome region 22q11.21-23, encodes for the catechol-O-methyltransferase enzyme, responsible for catalyzing the O-methylation reaction of the catecholamines, among which dopamine is included. This is the principal pathway of degradation of this neurotransmitter. The study of the genetic variants of COMT and its role as pharmacogenetic biomarker arises from the importance of this function, which makes it one of the candidate genes for schizophrenia.[110]

The COMT gene contains a polymorphism, Val158Met in which the Met allele seems to be associated with diminished enzyme activity which would, thus, give rise to an accumulation of dopamine in the synaptic space.

Regarding the pharmacogenetic importance of this gene, a first study conducted in Asian patients concluded that the Val158Met change was not associated with response to risperidone.[96] However, subsequent studies found an association between the slow-functioning metabolizer allele Met in homozygosis and resistance to first generation antipsychotics.[111, 112] On the contrary, this same allele has been related to greater efficacy of clozapine on the cognitive aspects of schizophrenia[113] and with better response to olanzapine, both on negative symptoms and on the alterations of the prefrontal cortex function and short term memory.[114, 115] In a recent work conducted in Spanish patients, Molero et al. indicated the existence of an association between the COMT genotype, severity of the psychotic symptoms and response to treatment with neuroleptics.[116]

In regards to the effect of the SNP Val158Met on the adverse reactions induced by antipsychotic treatment, a recent meta-analysis has demonstrated the association between tardive dyskinesia and this variation, concluding that the Met allele confers a protector effect against the appearance of this side effect. [117]

HOW WOULD PHARMACOGENETICS BENEFIT SCHIZOPHRENIA TREATMENT?

Although the idea of individualized medicine seems useful for all treatments, there is a group of therapies in which it takes on special importance: those in which there are severe and frequent side effects and in which dose optimization, using the trial and error method, would entail an excessively long period of time. Antipsychotic treatments entail both conditions. Most of the drugs used have a very narrow therapeutic window so that detection of the best dose is a difficult task. Months, and even years, may pass until achieving a correct treatment for the patient, a time in which the disease continues on its course. In schizophrenia, response time is especially important in the face of the first episode, not only for physical or biochemical reasons, but also because of the psychological impact that the disease has on the patient and his/her setting.[118]

a) In the disease setting and its treatment:
   It must be kept in mind that lack of antipsychotic response, especially in first episodes, and the high frequency of treatment-derived adverse effects are two of the causes of the elevated rate of treatment dropout,[17] largely determining the prognosis of the disease. It is very likely that lack of treatment, derived from these factors, is also responsible for the increase of mortality in schizophrenic patients.
   Therefore, the interest for pharmacogenetic studies in this therapeutic field has a clear objective: to identify those markers capable of predicting which treatment would produce the least side effects and the best clinical response. In this way, pharmacogenetics would help to increase treatment success by reducing stabilization time and dropout rates, collaborating, finally, to improve the prognosis of schizophrenic patients.
b) In the social-economic setting:
   It must be kept in mind that schizophrenia is a highly incapacitating disease with high prevalence[3] that entails high healthcare costs. It has been estimated that the total cost derived from schizophrenia in Spain is approximately 2000 million Euros annually.[119] This value includes the direct and indirect costs.
   It has been estimated that the direct costs derive from schizophrenia treatment accounts for approximately 1000 million Euros yearly, 2.7% of the healthcare budget, and essentially correspond to 3 categories: outpatient visits (approximately 33 million Euros per year), drug costs (approximately 250 million Euros) and hospital stays (approximately 760 million Euros).[119] It must be kept in mind that treatments with atypical antipsychotics are especially expensive and the acute phases generated by the first episodes and relapses generally require the patient to be admitted.
   The indirect costs are fundamentally paid by the patient's family and are principally due to the increase in mortality, dependant situation and low degree of social integration derived from the disease. Although they are difficult to quantify, it is estimated that this accounts for approximately one million Euros yearly.[119]
   Schizophrenic patients have a very short productive life:

schizophrenia is one of the main causes of discapacity and it is estimated that 84% of schizophrenic patients have a dependent-living situation.

The psychosocial aspect is also important in schizophrenic patients. There is evidence that therapies complementary to drug therapy (cognitive-behavioral, family, etc) help in the course of the disease. [120] These type of therapies also form a part of the indirect costs, since they are not always paid for by the healthcare systems.

Lack of treatment compliance derived both from the antipsychotic lack of efficacy and the appearance of adverse reactions contributes to increasing both direct and indirect costs.

It is not estimated that the introduction of pharmacogenetics is going to lead to an important decrease in the drug cost of schizophrenia, given that the treatments are, in many cases, chronic. However, being able to predict response and prevent the adverse effects derived from the treatment could help to reduce the number of hospital stays (most of the readmissions occur due to lack of treatment compliance or lack of efficacy) and their duration, as well as the indirect costs derived from the disease. The cost-effectiveness of a pharmacogenetic test depends, on the one hand, on the benefits, both economical (monetary units) and on quality of life of the patient (clinical units) and, on the other hand, on the cost of the application of the test *per se*. The cost of a pharmacogenetics test will depend largely on the cost of the genotyping. High-capacity genotyping techniques currently allow for a much lower per sample cost and the establishment of better technologies will help in the future to decrease these costs.

HOW SHOULD A PHARMACOKINETIC TEST BE FOR ANTIPSYCHOTIC DRUGS

An important point is what information should be included in a pharmacogenetic study of this type. Should it contain information on a single marker, above all the markers that participate in the response to a specific antipsychotic drug or should a more complete integration be sought?

Most of the scientific information available in this regards refers to the association of variations in individual genes with the response or with the appearance of adverse effects. However, since the response to antipsychotics is a complex process in which both pharmacokinetic and pharmacodynamic factors as well as environmental factors mediate, a simplistic study strategy (of one or very few markers) does not seem to be the most adequate. Thus, any pharmacogenetic test should include the study of genes involved in the pharmacokinetics and pharmacodynamics variability and should consider the population component.

In the specific case of schizophrenia, the elevated rate of drug replacements in the treatment [17] requires the pharmacogenetic analysis to include all those markers predictive of response and of adverse effects for all the commonly used antipsychotics in order to increase the utility of the information obtained.

Another point to keep in mind is the scaling capability of the genotyping method chosen. Both the pharmacogenomics and research in the new treatment fields may provide new data that will lead to recommending the addition of markers at a given time, so that the use of methods that not only allow for it, but also facilitate it, is recommended.

CAN A PHARMACOGENETIC TEST ALREADY BE CONDUCTED FOR ANTIPSYCHOTIC DRUGS?

In diseases such as cancer, the change of treatment or dose is made within very controlled methods and following very strict parameters of response, appearance of side effects, etc. The effects of poor drug adjustment may be fatal for the patient, either because it implies irreversible progression of the disease or due to the appearance of adverse reactions with important consequences. Thus, in this field, an almost total degree of safety in the pharmacogenetic prediction is necessary, as occurs in the case of UGT1A1 in the response to Irinotecan in colorectal cancer.[121]

However, the situation is different in the case of treatment with antipsychotics in schizophrenia: the initial choice of treatment is performed without using a pre-established physiopatological criterion, it being possible to vary the dose and drug depending on the prescribing physician. In this scenario, it seems reasonable to postulate the integration of pharmacogenetic studies into the daily clinical practice.

From the technological point of view, the necessary resources are currently available to conduct thousands of genotypes in a relative short time so that it would be useful for the psychiatrist, who needs to decide which drug and what dose is needed to treat a patient and this is especially important in first episodes. The advances in this field have been spectacular in these recent years. There are medium-throughput techniques such as SNaPshot minisequencing, high-throughput techniques as those based on the Maldi-TOF mass spectrometry[122] and even a group of genotyped and commercial chips, such as the Amplichip P450®, as if made to order. However, a pharmacogenetic test depends much more than on the quantitative capacity of the analysis. It must be known what to analyze and what the implication of this analysis would be.

Although many markers of response and side effects in the antipsychotic treatment have been identified by studies of association of different nature, most have been part of exploratory studies, and only some have been validated, as

for example that of the CYP2D6. Unfortunately, there is no "prime" marker and few studies have been replicated successfully. Thus, although the predictive value of most of the markers is limited, their use would be justified since this is a tool that can be used to seek improvement in the therapeutic intervention that would occur in any event, and for which there are alternatives.

The discrepancies between some association studies[77, 88] are probably due to differences in the characteristics of the sample used (differences on the clinical and/or population level). Furthermore, with exceptions, neither the studies based on genes of pharmacokinetic molecules (cytochromes) do include simultaneous analysis of pharmacodynamic genes (receptors), nor viceversa. This fact could also contribute to the appearance of discrepancies between studies and the lack of strength of their results, [123] given that the final response to treatment is mediated by both factors.

The inclusion of pharmacogenetic studies in clinical trials conducted prospectively, including a large number of patients, could, undoubtedly, significantly contribute to the development of personalized medicine protocols.

TRANSFER TO THE CLINICAL PRACTICE: A PHARMACOGENETIC REPORT

Some pharmacogenetic tests of different nature on the market (PHARMAchip of Progenika, DRUGINCODE of Ferrer inCode Amplichip P450 of Roche) are already offered. Even though some of them have been homologated for clinical use, their penetration into the market is still relatively limited. Undoubtedly, this is influenced by financial and technical questions, but fundamentally by knowledge. It is essential to implement the transfer of the results from the analysis of the genotypes of the patient to the clinician. It must not be overlooked that the final purpose of pharmacogenetics is to provide therapeutic action guidelines based on the analysis of the genetic variations. It is not sufficient to conclude that the patient has a poor metabolizer predictive phenotype or that his/her serotoninergic receptor has diminished function. Rather, it is necessary to establish what to do with these results, that is, finally, how to modify the treatment: increasing or decreasing the dose regarding the usual dose or switching drugs.[123, 122]

The enormous influence of the non-genetic factors in the final response must also be taken into account. These factors also may and should be taken into account in a pharmogenetic report.

ACKNOWLEDGEMENTS

This work has been partially financed by the intramural project 07/705.1 of CIBERER and by the DIANA-USC Program of the Fundación Barrié de la Maza

REFERENCES

1. Saha S, Chant D, Mcgrath J. Meta-analyses of the incidence and prevalence of schizophrenia: conceptual and methodological issues. Int J Methods psychiatr Res 2008;17(1):55-61.
2. OMS, 1960
3. Gutierrez-Recacha P, Chisholm D, Haro JM, Salvador-Carulla L, Ayuso-Mateos JL. Cost-effectiveness of different clinical interventions for reducing the burden of schizophrenia in Spain. Acta Psychiatr Scand 2006;114 (Suppl. 432):29-38.
4. Murray CJL, Lopez AD. The Global Burden Disease: A Comprehensive Assessment of Mortality and Disability From Diseases, Injuries, and Risk Factors in 1999 and Projected to 2020. Cambridge, MA, Harvard University Press, 1996.
5. Andlin- Sobocki P, Jönsson B, Wittchen H-U, Olesen j . Cost of Disorders of the Brain in Europe. European J Neurology 2005;12 (suppl 1):1-27.
6. Mueser KT, McGurk SR. Schizophrenia. Lancet 2004; 363(9426):2063-72.
7. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psych 1998;173:11-53.
8. American Psychiatric Association. Diagnosis and statistical manual of mental disorders, 4th ed. Washington DC: American Psychiatric Association, 1994.
9. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry 1994;151(10):1409-16.
10. Tandon R, Belmaker R, Gattaz W, Lopez-Ibor J, Okasha A, Singh B, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophrenia Research 2008;100(1-3):20-38.
11. Erik Johnsen, Hugo A. Jørgensen. Effectiveness of second generation antipsychotics: A systematic review of randomized trials. BMC Psychiatry 2008;8:31.
12. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60(6):553-64.
13. Ozdemir V, Aklillu E, Mee S, Bertilsson L, Albers LJ, Graham JE et al. Pharmacogenetics for off-patent antipsychotics: reframing the risk for tardive dyskinesia and access to essential medicines. Expert Opin Pharmacother 2006;7:119-33.
14. Dan Chisholm, Oye Gureje, Sandra Saldivia, Marcelo Villalón Calderón, Rajitha Wickremasinghe, et al. Schizophrenia treatment in the developing world: an interregional and multinational cost-effectiveness analysis. Bulletin of the World Health Organization 2008;86:542-51.
15. Weiden PJ & Olfson M. Cost of relapse in schizophrenia. Schizophr Bull 1995;21(3):419-29.
16. Wyatt RJ, Henter ID. The effects of early and sustained intervention on the long-term morbidity of schizophrenia. J Psychiatr Res 1998;32(3-4):169-77.
17. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia Clinical Antipsychotic. Trials of Intervention Effectiveness (CATIE) Investigators. N Engl J Med 2005;353(12):1209-23.
18. Lieberman JA. What the CATIE study means for clinical practice. Psychiatr Serv 2006;57(8):1075
19. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res 2004:15;72(1):41-51.
20. Carpenter WT Jr, Strauss JS, Bartko JJ. Flexible system for the diagnosis of schizophrenia: report from the WHO International

Pilot Study of Schizophrenia. Science 1973; 21;182(118):1275-8.
21. Comittee for medicinal products for human use European Medicines Agency (CHMP). Reflection paper on the use of pharmacogenetics in the pharmacokinetic evaluation of Medicinal Products. European Medicines Agency (EMEA) 2007.
22. Mahgoub A, Idle JR, Dring DG, et al. Polymorphic hydroxylation of debrisoquine in man. Lancet 1977;2:584-6.
23. De Leon J, Diaz FJ, Rogers T, Browne D, Dinsmore L, Ghosheh O, et al. A pilot study of plasma caffeine concentrations in a US sample of smokers and non-smoker volunteers. Prog Neuro-Psychopharmacol Biol Psychiatry 2003;27:165-71.
24. Bertilsson L, Carrillo JA, Dahl ML et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. Br J Clin Pharmacol 1994;38:471-3.
25. De Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. Psychiatr Serv 2004;55:491-3.
26. Chiu CC, Lane H, Huang M, Liu H, Jann M, Hon Y, et al. Dose-Dependent Alternations in the Pharmacokinetics of Olanzapine During Coadministration of Fluvoxamine in Patients With Schizophrenia. The Journal of Clinical Pharmacology 2004;44(12):1385-90.
27. Jeppsen U, Gram LF, Vistisen K, Loft S, Poulsen HE, Brosen K.Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. Eur J Clin Pharmacol 1996;51:73-8.
28. Van der Weide J, Steijns LS, van Weelden MJ. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. Pharmacogenetics 2003;13:169-72.
29. Doude van Troostwijk LJ, Koopmans RP, Vermeulen HD, Guchelaar HJ. CYP1A2 activity is an important determinant of clozapine dosage in schizophrenic patients. European Journal of Pharmaceutical Sciences 2003;20:451-7.
30. Shirley K, Hon Y, Penzak S, Lam Y, Spratlin V, Jann M. Correlation of Cytochrome P450 (CYP) 1A2 Activity Using Caffeine Phenotyping and Olanzapine Disposition in Healthy Volunteers. Neuropsychopharmacology 2002;28:961-6.
31. http://www.cypalleles.ki.se/
32. Sachse C, Brockmoller J, Bauer S, Roots I. Functional significance of a C-->A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 1999 Apr; 47(4):445-9.
33. Tucker GT, Silas JH, Iyun AO, Lennard MS, Smith AJ. Polymorphic hydroxylation of debrisoquine. Lancet 1977;2:718.
34. Eichelbaum M, Spannbrucker N, Steinke B, Dengler HJ. Defective N-oxidation of sparteine in man: a new pharmacogenetic defect. Eur J Clin Pharmacol 1979;16:183-7.
35. Rau T, Wohlleben G, Wuttke H, Thuerauf N, Lunkenheimer J, Lanczik M, Eschenhagen T. CYP2D6 genotype: impact on adverse effects and nonresponse during treatment with antidepressants-a pilot study. Clin Pharmacol Ther 2004;75(5):386-93.
36. Thuerauf N, Lunkenheimer J. The impact of the CYP2D6-polymorphism on dose recommendations for current antidepressants. Eur Arch Psychiatry Clin Neurosci 2006 Aug;256(5):287-93.
37. Griese EU, Zanger UM, Brudermanns U, Gaedigk A, Mikus G, Morike K, et al. Assessment of the predictive power of genotypes for the in-vivo catalytic function of CYP2D6 in a German population. Pharmacogenetics 1998;8(1):15-26.
38. Dahl ML, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjoqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish population. Analysis of the molecular genetic basis. J Pharmacol Exp Ther 1995 Jul;274(1):516-20.
39. Johansson I, Lundqvist E, Bertilsson L, Dahl ML, Sjoqvist F, Ingelman-Sundberg M. Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. Proc Natl Acad Sci U S A 1993;90(24):11825-9.
40. Sachse C, Brockmöller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet 1997;60:284-95.
41. Kubota T, Yamaura Y, Ohkawa N, Hara H, Chiba K. Frequencies of CYP2D6 mutant alleles in a normal Japanese population and metabolic activity of dextromethorphan O-demethylation in different CYP2D6 genotypes.Br J Clin Pharmacol 2000;50:31-4.
42. Griese EU, Asante-Poku S, Ofori-Adjei D, Mikus G, Eichelbaum M. Analysis of the CYP2D6 gene mutations and their consequences for enzyme function in a West African population. Pharmacogenetics 1999;9:715-23.
43. Menoyo A, del Rio E, Baiget M. Characterization of variant alleles of cytochrome CYP2D6 in a Spanish population. Cell Biochem Funct 2006;24:381-5.
44. Bork J, Rogers T, Wedlund P, de Leon J. A pilot study of risperidone metabolism: the role of cytochrome P450 2D6 and 3A. J Clin Psychiatry 1999;60:469-76.
45. De Leon J, Susce MT, Pan RM, Fairchild M, Koch W, Wedlund PJ. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. J Clin Psychiatry 2005;66:15-27.
46. Guzey C, Aamo T, Spigset O. Risperidone metabolism and the impact of being a cytochrome P450 2D6 ultrarapid metabolizar (letter). J Clin Psychiatry 2000;61:600-1.
47. Albrecht A, Morena PG, Baumann P, Eap CB. High dose of depot risperidone in a nonresponder schizophrenic patient. J Clin Psychopharm 2004;24:673-4.
48. Bergmann TK, Bathum L, Brosen K. Duplication of CYP2D6 predicts high clearance of desipramine, but high clearance does not predict duplication of CYP2D6. Eur J Clin Pharmacol 2001;57:123-27.
49. Gunasekara N S & Spencer C M. Quetiapine - a review of its use in schizophrenia. CNS Drugs 1998;9(4):325-40.
50. Prakash C, Kamel A, Cui D, Whalen RD, Miceli JJ, Tweedie D. Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. Br J Clin Pharmacol 2000;49 Suppl 1:35S-42S.
51. Ozdemir V, Kalowa W, Tang BK, Paterson AD, Walker SE, Endrenyi L, et al. Evaluation of the genetic component of variability in CYP3A4 activity: a repeated drug administration method. Pharmacogenetics 2000;10:373-88.
52. Wandel C, Witte JS, Hall JM, Stein CM, Wood AJ, Wilkinson GR. CYP3A activity in African American and European American men: population differences and functional effect of the CYP3A4 1B 5'-promoter region polymorphism. Clin Pharmacol Ther 2000;68:288-94.
53. Sinues B, Vicente J, Fanlo A, Vasquez P, Medina JC, Mayayo E, et al. CYP3A5*3 and CYP3A4*1B allele distribution and genotype combinations: differences between Spaniards and Central Americans. Ther Drug Monit 2007;29(4):412-6.
54. Food and Drug Administration: Center for Drug Evaluation and Research Briefing Information for Psychopharmacologic Drugs Advisory Committee Meeting. July 2000.
55. Kohlrausch FB, Gama CS, Lobato MI, Belmonte-de-Abreu P, Callegari-Jacques SM, Gesteira A, et al. Naturalistic pharmacogenetic study of treatment resistance to typical neuroleptics in European-Brazilian schizophrenics. Pharma-

cogenet Genomics 2008;18(7):599-609.
56. Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001;27(4):383-91.
57. Gervasini G, Vizcaino S, Gasiba C, Carrillo JA, Benitez J. Differences in CYP3A5*3 Genotype Distribution and Combinations With Other Polymorphisms Between Spaniards and Other Caucasian Populations. Ther Drug Monit 2005;27:819–21.
58. Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov 2004;3(4):353-9.
59. Hazelwood LA, Sanders-Bush E. His452Tyr Polymorphism in the Human 5-HT2A Receptor Destabilizes the Signaling Conformation Mol Pharmacol 2004;66:1293–300.
60. Masellis M, Basile V, Meltzer HY, Lieberman JA, Sevy S, Macciardi FM, et al. Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology 1998;19:123-32.
61. Arranz MJ, Collier D, Sodhi M, Ball D, Roberts G, Price J, et al. Association between clozapine response and allelic variation in 5-HT2A receptor gene. Lancet 1995;346:281-2.
62. Arranz MJ, Collier D, Munro J, Sham P, Kirov G, Sodhi M, et al. Analysis of a structural polymorphism in the 5-HT2A receptor and clinical response to clozapine. Neurosci Lett 1996 Oct 18;217(2-3):177-8.
63. Arranz MJ, Munro J, Owen MJ, Spurlock G, Sham PC, Zhao J, et al. Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol Psychiatry 1998;3:61-6.
64. Arranz MJ, Munro J, Sham P, Kirov G, Murray RM, Collier DA, et al. Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. Schizophrenia Research 1998;32:93-9.
65. Inayama Y, Yoneda H, Sakai T, Ishida T, Nonomura Y, Kono Y, et al. Positive association between a DNA sequence variant in the serotonin 2A receptor gene and schizophrenia. Am J Med Genet 1996 Feb 16;67(1):103-5.
66. Erdmann J, Shimron-Abarbanell D, Rietschel M, Albus M, Maier W, Korner J, et al. Systematic screening for mutations in the human serotonin-2A (5-HT2A) receptor gene: identification of two naturally occurring receptor variants and association analysis in schizophrenia. Hum Genet 1996;97(5):614-9.
67. Malhotra AK, Goldman D, Ozaki N, Breier A, Buchanan R, Pickar D. Lack of association between polymorphisms in the 5-HT2A receptor gene and antipsychotic response to clozapine. Am J Psychiatry 1996;153:1092-4.
68. Joober R, Benkelfat C, Brisebois K, Toulouse A, Turecki G, Lal S, et al. T102C polymorphism in the 5HT2A gene and schizophrenia: relation to phenotype and drug response variability. J Psychiatry Neurosci 1999 Mar;24(2):141-6.
69. Anttila S, Kampman O, Illi A, Rontu R, Lehtimäki T, Leinonen E. Association between 5-HT2A, TPH1 and GNB3 genotypes and response to typical neuroleptics: a serotonergic approach BMC Psychiatry 2007 May 23;7:22.
70. Lattuada E, Cavallaro R, Serretti A, Lorenzi C, Smeraldi E. Tardive dyskinesia and DRD2, DRD3, DRD4, 5-HT2A variants in schizophrenia: an association study with repeated assessment. Int J Neuropsychopharmacol 2004;7(4):489-93.
71. Ellingrod VL, Lund BC, Miller D, Fleming F, Perry P, Holman TL, et al. 5-HT2A receptor promoter polymorphism, -1438G/A and negative symptom response to olanzapine in schizophrenia. Psychopharmacol Bull 2003;37(2):109-12.
72. Polesskaya OO, Aston C, Sokolov BP. Allele C-specific methylation of the 5-HT2A receptor gene: evidence for correlation with its expression and expression of DNA methylase DNMT1. J Neurosci Res 2006;83(3):362-73.
73. Sodhi MS, Arranz MJ, Curtis D, Ball DM, Sham P, Roberts GW, et al. Association between clozapine response and allelic variation in the 5-HT2C receptor gene. NeuroReport 1995;7:169-72.
74. Malhotra AK, Goldman D, Ozaki N, Rooney W, Clifton A, Buchanan RW, et al. Clozapine response and the 5HT2C Cys23Ser polymorphism. Neuroreport 1996a; 2;7(13):2100-2.
75. Rietschel M, Naber D, Fimmers R, Moller HJ, Propping P, Nothen MM. Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. Neuroreport 1997;27;8(8):1999-2003.
76. Arranz MJ, Bolonna AA, Munro J, Curtis CJ, Collier DA, Kerwin RW. The serotonin transporter and clozapine response. Mol Psychiatry 2000a;5:124-5.
77. Arranz MJ, Munro J, Birkett J, Bolonna A, Mancama D, Sodhi M, et al. Pharmacogenetic prediction of clozapine response. Lancet 2000b;355:1615-6.
78. Veenstra-VanderWeele J, Anderson GM, Cook EH. Pharmacogenetics and the serotonin system: initial studies and future directions. Eur J Pharmacol 2000;410:165-81.
79. Yuan X, Yamada K, Ishiyama-Shigemoto S, Koyama W, Nonaka K. Identification of polymorphic loci in the promoter region of the serotonin 5-HT2C receptor gene and their association with obesity and type II diabetes. Diabetologia 2000;43:373-6.
80. Reynolds GP, Templeman LA, Zhang ZJ. The role of 5-HT2C receptor polymorphisms in the pharmacogenetics of antipsychotic drug treatment. Prog Neuropsychopharmacol Biol & Psychiatry 2005 Jul;29(6):1021-8.
81. Eberle-Wang K, Lucki I, Chesselet MF. A role for the subthalamic nucleus in 5-HT2C-induced oral dyskinesia. Neuroscience 1996;72:117-28.
82. Ellingrod VL, Perry PJ, Ringold JC, Lund BC, Bever-Stille K, Fleming F, et al. Weight gain associated with the -759C/T polymorphism of the 5HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet 2005 Apr 5;134B(1):76-8.
83. Miller DD, Ellingrod VL, Holman TL, Buckley PF, Arndt S. Clozapine-induced weight gain associated with the 5HT2C receptor -759C/T polymorphism. Am J Med Genet B Neuropsychiatr Genet 2005 Feb 5;133B(1):97-100.
84. Templeman LA, Reynolds GP, Arranz B, San L. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. Pharmacogenet Genomics 2005;15(4):195-200.
85. Tsai SJ, Hong CJ , Yu YW , Lin CH , Song HL, Lai HC, et al. Association study of a functional serotonin transporter gene polymorphism with schizophrenia, psychopathology and clozapine response. Schizophr Res 2000;44:177-81.
86. Wang L, Yu L, He G, Zhang J, Zhang AP, Du J, et al. Response of risperidone treatment may be associated with polymorphisms of HTT gene in Chinese schizophrenia patients. Neuroscience Letters 2004;414:1-4.
87. Arrang JM. Histamine and schizophrenia. Int Rev Neurobiol 2007;78:247-87.
88. Schumacher J, Schulze T, Wienker T, Rietschel M, Nothen M. Pharmacogenetics of clozapine response. Lancet 2000;356:506-7.
89. Rao PA, Pickar D, Gejman PV, Ram A, Gershon ES, Gelernter J. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. Arch Gen Psych 1994;51:912-7.
90. Rietschel M, Naber D, Oberlander H, Holzbach R, Fimmers R, Eggermann K, et al. Efficacy and side-effects of clozapine:

Testing for association with allelic variation in the dopamine D4 receptor gene. Neuropsychopharmacology 1996;15:491-6.
91. Shaikh S, Collier D, Kerwin RW, Pilowsky LS, Gill M, Xu WM, et al. Dopamine D4 receptor subtypes and response to clozapine. Lancet 1993;341:116.
92. Crocq MA, Gill M, Kerwin R. Analysis of clozapine response and polymorphisms of the dopamine D4 receptor gene (DRD4) in schizophrenic patients. Neuropsych Genetics 1995;60:541-5.
93. Arinami T, Gao M, Hamaguchi H, Toru M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum Mol Genet 1997;6:577-82.
94. Lencz T, Robinson DG, Xu K, Ekholm J, Sevy S, Gunduz-Bruce H, et al. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. Am J Psychiatry 2006;163(3):529-31.
95. Thompson J, Thomas N, Singleton A, Piggot M, Lloyd S, Perry EK et al. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics 1997;7:479-84.
96. Yamanouchi Y, Iwata N, Suzuki T, Kitajima T, Ikeda M, Ozaki N. Effect of DRD2, 5-HT2A, and COMT genes on antipsychotic response to risperidone. Pharmacogenomics J 2003;3(6):356-61.
97. Lane HY, Lee CC, Chang YC, Lu CT, Huang CH, Chang WH: Effects of dopamine D2 receptor Ser311Cys polymorphism and clinical factors on risperidone efficacy for positive and negative symptoms and social function. Int J Neuropsychopharmacol 2004;7(4):461-70.
98. Xing Q, Qian X, Li H, Wong S, Wu S, Feng G, et al. The relationship between the therapeutic response to risperidone and the dopamine D2 receptor polymorphism in Chinese schizophrenia patients. Int J Neuropsychopharmacol 2007 Oct;10(5):631-7.
99. Zai CC, De L, V, Hwang RW, et al. Meta-analysis of two dopamine D2 receptor gene polymorphisms with tardive dyskinesia in schizophrenia patients. Mol Psychiatry 2007;12:794-5.
100. Bakker PR, van Harten PN, van Os J. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. Mol Psychiatry 2008;13(5):544-56.
101. Staddon S, Arranz MJ, Mancama D, Mata I, Kerwin RW. Clinical applications of pharmacogenetics in psychiatry. Psychopharmacology (Berl) 2002 Jun;162(1):18-23.
102. Adams DH, Close S, Farmen M, Downing AM, Breier A, Houston JP. Dopamine receptor D3 genotype association with greater acute positive symptom remission with olanzapine therapy in predominately caucasian patients with chronic schizophrenia or schizoaffective disorder. Hum Psychopharmacol 2008;23(4):267-74.
103. Steen VM, Løvlie R, MacEwan T, McCreadie RG. Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. Mol Psychiatry 1997 Mar;2(2):139-45.
104. Lerer B, Segman RH, Fangerau H, Daly AK, Basile VS, Cavallaro R, et al. Pharmacogenetics of tardive dyskinesia: combined analysis of 780 patients supports association with dopamine D3 receptor gene Ser9Gly polymorphism. Neuropsychopharmacology 2002 Jul;27(1):105-19.
105. Bakker PR, van Harten PN, van Os J. Antipsychotic-induced tardive dyskinesia and the Ser9Gly polymorphism in the DRD3 gene: a meta analysis. Schizophr Res 2006 Apr;83(2-3):185-92.
106. Eichhammer P, Albus M, Borrmann-Hassenbach M, Schoeler A, Putzhammer A, Frick U, et al. Association of dopamine D3-receptor gene variants with neuroleptic induced akathisia in schizophrenic patients: a generalization of Steen's study on DRD3 and tardive dyskinesia. Am J Med Genet 2000 Apr 3;96(2):187-91.
107. Boulton DW, DeVane CL, Liston HL, and Markowitz JS. In vitro P- glycoprotein affinity for atypical and conventional antipsychotics. Life Sci 2002;71:163-9.
108. Xing Q, Gao R, Li H, Feng G, Xu M, Duan S et al. Polymorphisms of the ABCB1 gene are associated with the therapeutic response to risperidone in Chinese schizophrenia patients. Pharmacogenomics 2006;7:987-93.
109. Bozina N, Kuzman MR, Medved V, Jovanovic N, Sertic J, Hotujac L. Associations between MDR1 gene polymorphisms and schizophrenia and therapeutic response to olanzapine in female schizophrenic patients. J Psychiatr Res 2008 Jan;42(2):89-97.
110. Glatt SJ, Faraone SV, Tsuang MT. Association between a functional catechol O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. Am J Psychiatry 2003;160:469-76.
111. Inada T, Nakamura A, Iijima Y. Relationship between catechol-O-methyltransferase polymorphism and treatment-resistant schizophrenia. Am J Med Genet 2003;120:35-9.
112. Anttila S, Illi A, Kampman O, Mattila KM, Lehtimäki T, Leinonen E. Interaction between NOTCH4 and catechol-O-methyltransferase genotypes in schizophrenia patients with poor response to typical neuroleptics. Pharmacogenetics 2004;14(5):303-7.
113. Woodward ND, Jayathilake K, Meltzer HY. COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia. Schizophrenia Research 2007;90(1-3):86-96.
114. Bertolino A, Caforio G, Blasi G, De Candia M, Latorre V, Petruzzella V, et al. Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. Am J Psychiatry 2004;161:1798-805.
115. Bertolino A, Caforio G, Blasi G, Rampino A, Nardini M, Weinberger DR, et al. COMT Val158Met polymorphism predicts negative symptoms response to treatment with olanzapine in schizophrenia. Schizophrenia Research 2007;95:253-5.
116. Molero P, Ortuño F, Zalacain M, Patiño-García A. Clinical involvement of catechol-O-methyltransferase polymorphisms in schizophrenia spectrum disorders: influence on the severity of psychotic symptoms and on the response to neuroleptic treatment.Pharmacogenomics J 2007;7(6):418-26.
117. Bakker PR, van Harten PN, van Os J. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. Mol Psychiatry 2008;13(5):544-56.
118. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry 2006;163(4):743-5.
119. Juan Oliva-Moreno, Julio López-Bastida, Rubén Osuna-Guerrero, Ángel Luis Montejo-González y Beatriz Duque-González. The costs of schizophrenia in Spain. Eur J Health Econ 2006;7(3):179-84.
120. Penn DL, Waldheter EJ, Perkins DO,Mueser KT, Lieberman JA. Psychosocial Treatment for First-Episode Psychosis. A Research Update. Am J Psychiatry 2005;162:2220-32.
121. Iyer L, Ratain MJ. Pharmacogenetics and cancer chemotherapy. Eur J Cancer 1998;34:1493-9.
122. Gesteira A. Diseño y desarrollo de un programa de Farmacogenética en antipsicóticos enfocado al tratamiento de la esquizofrenia. Traslación a la práctica clínica de la información farmacogenética. Tesis Doctoral. Universidad de Santiago de Compostela 2008. ISBN: 978-84-9887-112-8.
123. Grossman I, Sullivan PF, Walley N, Liu Y, Dawson JR, Gumbs

C, et al. Genetic determinants of variable metabolism have little impact on the clinical use of leading antipsychotics in the CATIE study. Genet Med 2008;10(10):720-9.

124. de Leon J, Armstrong SC, Cozza KL. The dosing of atypical antipsychotics. Psychosomatics 2005;46(3);262-73.