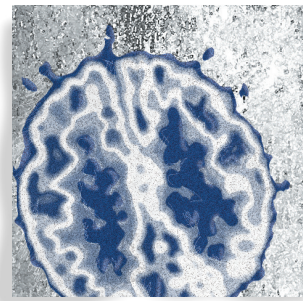


## *Pharmacogenomics of antidepressant treatment effects*

*Julio Licinio, MD; Ma-Li Wong, MD*



*There has been considerable promise and hope that pharmacogenomics will optimize existing treatments for major depression, as well as identify novel targets for drug discovery. Immediately after the sequencing of the human genome, there was much hope that tremendous progress in pharmacogenomics would rapidly be achieved. In the past 10 years this initial enthusiasm has been replaced by a more sober optimism, as we have gone a long way towards the goal of guiding therapeutics based on genomics. While the effort to translate discovery to clinical applications is ongoing, we now have a vast body of knowledge as well as a clear direction forward. This article will provide a critical appraisal of the state of the art in the pharmacogenomics of depression, both in terms of pharmacodynamics and pharmacokinetics.*

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In a landmark article published in 2004, Lawrence J. Lesko and Janet Woodcock, from the United States Food and Drug Administration (FDA), defined pharmacogenomics broadly as “the study of inter-individual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers and alterations in gene expression or inactivation that might be correlated with pharmacological function and therapeutic response.” They wisely stated that “translating pharmacogenomics from bench to bedside (or from discovery to marketability) is a multidisciplinary problem that involves addressing philosophical, societal, cultural, behavioral and educational differences between the private and public sector, as well as issues unique to drug development, extent of scientific expertise, interdisciplinary communication and clinical practice.”<sup>1</sup>

Examining the statement above, we see the phrase “pharmacological function and therapeutic response.” This can be dissected into two major elements: pharmacokinetics and pharmacodynamics. We believe that it is always useful to conceptualize pharmacology in terms of thinking of what happens to a drug from when it first enters the body to when it is disposed of (excreted).

**Keywords:** *depression; antidepressant; genetics; pharmacogenomics; serotonin transporter (SLC6A4); adverse reaction; drug target; therapeutics*

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There are three steps in this trajectory:

- Drug absorption
- Drug disposition
- Drug effect.

The first two processes are in the realm of pharmacokinetics, defined as the process by which a drug is absorbed, distributed, metabolized, and eliminated. The proteins involved and the genes that encode them regulate the velocity and amount of drug that circulates through the body and that enters the target tissue(s). Drug effect, in contrast, is in the realm of pharmacodynamics, which according to Dokoumetzidis et al “is the most complex process during the presence of the drug in the human body. The drug can interact with various physiological systems and thus it is not uncommon for the pharmacodynamic response to be, in reality, nonlinear and governed by mechanisms that have not been studied extensively.”<sup>2</sup>

Pharmacogenomics applied to depression—as well as to all other diseases—faces a major obstacle: how to move from research efforts to widespread clinical use. This has two different elements:

- *First challenge:* The quality and replicability of the research findings. Are they robust enough to guide clinical practice?
- *Second challenge:* The very real gap between robust, universally accepted research findings and changes based on them to clinical guidelines and practice.

In the case of major depression, the two challenges above are distributed along the domains of pharmacodynamics and pharmacokinetics. The first challenge, related to the replicability and robustness of research findings, is applicable to the pharmacodynamic side of the pharmacogenomics of depression. The findings on the pharmacokinetic side, in contrast, are for the most part universally accepted, and face the second challenge, which is the grievous gap in translation from solid research to clinical use (*Table I*).

## The genetic basis of drug effects: pharmacodynamics

The genetic basis of drug effects is the pharmacodynamic domain of the pharmacogenomics of antidepressants. There has been considerable research in this area, with variable and sometimes contradictory results. As the body of evidence increases, some trends and findings become more solidly established, while other leads turn out to be increasingly harder to confirm.

## Serotonin transporter gene promoter polymorphism

The serotonin (5-HT) transporter gene promoter polymorphism (5-HTTLPR) has been the most studied genetic factor in association with antidepressant response. This line of inquiry has an interesting history. In 1993 Karl-Peter Lesch and colleagues published, in *Science*, a paper that has been cited over 2000 times, describing an association of anxiety-related traits with a polymorphism in the serotonin (5-HT) transporter gene regulatory region (5-HTTLPR).<sup>3</sup> Their findings were of great interest to the field: the regulatory (promoter) region of 5-HTTLPR has an insert/delete region of 44 nucleotides. The short variant of the polymorphism reduces the transcriptional efficiency of the 5-HTT gene promoter, resulting in decreased 5-HTT expression and 5-HT uptake. Additional work showed that this promoter has several other variants that may affect function<sup>4</sup>; some of those, such as rs25531, initially thought to be located just upstream of 5-HTTLPR<sup>5</sup> and an A/G SNP within the 5-HTTLPR,<sup>6</sup> turn out to be the same variant, described independently by different groups.<sup>7</sup>

Lesch et al’s original paper has led to a body of work on the 5-HTTLPR with 894 papers published to date, making it the most intensively studied genetic variation in psychiatry. Even though there are discrepant results, the body of existing work to date appears to indicate that high-expressing 5-HTTLPR alleles are associated with increased serotonin transporter binding in the living human brain.<sup>8</sup> A considerable level of quality of positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging studies is required to detect such in vivo effects of 5-HTTLPR.

The principle of reuptake of monoamines at the synaptic cleft was discovered by Nobel Laureate Julius Axelrod and described in 1961.<sup>9,10</sup> Most antidepressants used today are monoamine reuptake inhibitors, and act at the level of presynaptic transporters. Therefore, the

Replicability and robustness of findings	Gap from accepted findings to clinical use
Domain	
Pharmacodynamics	Pharmacokinetics
Genetic basis of drug effects	Genetics of drug absorption Genetics of drug disposition

Table I. Pharmacogenomics of depression.

monoamine transporters, such as 5-HTTLPR, which promote presynaptic reuptake of secreted amines, are the most logical candidate genes in pharmacogenomic studies of antidepressant treatment. Based on the work of Lesch and colleagues and on the fact that the selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressants, Smeraldi et al published, in *Molecular Psychiatry* in 1998, a seminal paper in which they show that those with at least one long allele of 5-HTTLPR had a better therapeutic response to fluvoxamine.<sup>11</sup> This was the first published report of a pharmacogenetic effect of a promoter sequence on treatment responses in all of medicine.

That initial paper led to a novel body of work, conducted independently by multiple groups from around the world, addressing the specific topic of how 5-HTTLPR variations are associated with antidepressant response. Today, a PubMed search on 5-HTTLPR and antidepressants shows 106 articles. In 2006 Serretti conducted a formal meta-analysis of published reports of the association of 5-HTTLPR with SSRI efficacy in depression. Fifteen studies with data from 1435 patients qualified to be in that meta-analysis. Three phenotypes were tested: remission rate, response rate, and response rate within 4 weeks. There was a significant association of the s/s variant of 5-HTTLPR with remission rate ( $P < 0.0001$ ) and both s/s and s/l variants with response rate ( $P = 0.0002$ ). Response rate within 4 weeks was associated in both models ( $P = 0.003$ – $P < 0.00001$ ).<sup>12</sup> In subsequent systematic reviews Horstmann and Binder identified 27 pharmacogenetic studies of the association of 5-HTTLPR and treatment response,<sup>13</sup> while Porcelli et al identified 58 such studies.<sup>14</sup> The overall conclusions are as follows: in Caucasian samples those with at least one *l* allele of 5-HTTLPR have a better, more accelerated response to antidepressants. In contrast, results in East Asian populations are more heterogeneous and conflicting, with some studies supporting *better* outcomes in those with the *s* alleles,<sup>15–18</sup> other studies supporting no effects for 5-HTTLPR,<sup>19,20</sup> and still other studies showing outcomes similar to those of Western populations; ie, better antidepressant response associated with the *l* allele.<sup>21–24</sup>

Additionally, another meta-analysis conducted by Kato and Serretti focused on 5-HTTLPR effects on antidepressant-induced adverse drug reactions (ADRs).<sup>25</sup> Data pooled from nine studies with 2642 subjects showed that those with the *l* allele had reduced rates of ADRs (0.64, CI: 0.49–0.82,  $P = 0.0005$ ).

### Other polymorphisms associated with antidepressant response

The most recent formal meta-analysis of pharmacogenetic findings in depression<sup>25</sup> showed that, in addition to 5-HTTLPR, the following genes affect antidepressant treatment response:

- Tryptophan hydroxylase 1 (TPH1) 218C/C genotype (7 studies, 754 subjects): significantly associated with a better response (odds ratio, OR=1.62;  $P = 0.005$ ), with no heterogeneity between ethnicities
- Met variant within the brain-derived natriuretic factor (BDNF) 66Val/Met polymorphism (4 studies, 490 subjects): also significantly associated with a better response OR=1.63,  $P = 0.02$ .

In terms of ADRs, pooled odds-ratios (ORs) of the following two genetic variants were shown by Kato and Serretti to be associated with a significant risk modulation<sup>25</sup>:

- 5-HTTLPR *l* (9 studies, 2642 subjects; OR=0.64,  $P = 0.0005$ )
- Serotonin receptor 2A (HTR2A) –1438G/G (7 studies, 801 subjects; OR=1.91,  $P = 0.0006$ ).

As expected, the level of significance became even higher when the analysis was restricted only to patients taking SSRIs (5-HTTLPR:  $P = 0.0001$ , HTR2A:  $P < 0.0001$ ).

Horstmann and Binder did a more descriptive but highly detailed synthesis of existing findings.<sup>13</sup> They stratified genes based on whether the aggregate of existing studies enrolled (i) more than 2000 patients; (ii) fewer than 2000 patients; (iii) fewer than 1000 patients, but with evidence of at least one independent replication; and (iv) genes with positive, single positive association reports. *Table II* summarizes their comprehensive survey of the existing literature.

In addition to the genes listed in *Table II*, Horstmann and Binder also identified the following genes, for which there are only single, positive association reports: 5-HT3A (serotonin receptor 3A, study N=100),<sup>26</sup> SLC6A3 (dopamine transporter, study N=190),<sup>27</sup> HSPA1A, HSPA1L (heat shock 70 kDa protein 1A and 1L, study N=142),<sup>28</sup> p75 (p75 neutrophin receptor, study N=228),<sup>29</sup> MAO-B (monoamine oxidase B, study N = 76),<sup>30</sup> CRHR2 (corticotropin-releasing hormone 2, study N=159),<sup>31</sup> GSK3B (glycogen synthase kinase-3 beta, study N=168),<sup>32</sup> KCNK2 (TREK1) (potassium channel, subfamily K, member 2, study N=751),<sup>33</sup> SERPINE1 (plasminogen activator inhibitor type 1, study N=140),<sup>34</sup> ADRA2A

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(alpha 2A-adrenergic receptor, study N=93),<sup>35</sup> *CNR1* (cannabinoid receptor 1, study N=141),<sup>36</sup> and *PSMB4*, *TBX21*, *STAT3* (inflammation-related genes).<sup>37</sup>

In summary, in the pharmacodynamic domain, variations in four genes have been shown in research studies totaling at least 1500 people each to be associated with antidepressant treatment response. They are the serotonin transporter gene promoter polymorphism (*5-HTTLPR*), FK506 binding protein 5 (*FKBP5*), glutamate receptor, ionotropic, kainate 4 (*GRIK4*), and serotonin receptor 2A (*HTR2A*). However, as can be seen in *Table II*, there are enough conflicting results that make these findings not yet ready for universal acceptance. A key question that is emerging is the following: are we ready to translate existing findings to the clinic, or is further investigative work still required to clarify the role of these genes in antidepressant response before translation can occur?

## Genetics of drug absorption and disposition: pharmacokinetics

It makes intuitive and scientific sense for us to assume that the genetics underlying drug disposition (pharmaco-

kinetics) will contribute to bioavailability at the site of the action, where pharmacodynamic effects occur. Two types of enzyme families are most important in this realm to affect antidepressant bioavailability: (i) the cytochrome P450 (CYP450) superfamily that regulates the degradation of antidepressants: and (ii) the superfamily of ATP binding cassette (ABC) transporter enzymes that regulate entry of certain antidepressants from the bloodstream into brain parenchyma, across the blood-brain barrier (BBB). The major P-glycoprotein, a 170-KDa glycoprotein encoded by the *ABCB1* (also known as MDR1—multi drug resistance 1) gene, has a role in the pharmacogenomics of antidepressants through its effects on the entry of antidepressant substrates (such as the tricyclics, citalopram, venlafaxine, and paroxetine) into the brain<sup>38,39</sup>; however the findings in this area have been contradictory.<sup>40</sup> In contrast, the data on the effects of CYP450 enzymes on the bioavailability of antidepressant drugs are very well established.

The pharmacogenetic effects of CYP450 have been reviewed elsewhere.<sup>41,42</sup> Among CYP450 enzymes, CYP2D6—and to a lesser degree CYP2C19—are the most important for antidepressant metabolism. For that

Gene (abbreviation) (full name)	Positive association		No association	
	Number of studies	Number of subjects	Number of studies	Number of subjects
<b>Genes with replicated evidence from studies with a total N of more than 2000</b>				
<i>FKBP5</i> FK506 binding protein 5	4	1524	3	1030
<i>GRIK4</i> Glutamate receptor, ionotropic, kainate 4	2	2203	0	0
<i>HTR2A</i> Serotonin receptor 2A	8	3556	5	555
<b>Genes with replicated evidence from studies with a total N of less than 2000</b>				
<i>COMT</i> Catechol-O-methyltransferase	6	834	1	334
<i>HTR1A</i> Serotonin receptor 1A	3	635	5	941
<i>BDNF</i> Brain-derived neurotrophic factor 1	3	591	2	856
<i>TPH1</i> Tryptophan hydroxylase 1	5	453	4	638
<i>GNB3</i> G-protein beta 3	3	684	4	630
<b>Genes with at least one independent replication and a total N of less than 1000</b>				
<i>TPH2</i> Tryptophan hydroxylase 2	1	182	1	96
<i>CRHR1</i> Corticotropin releasing hormone receptor 1	2	207	1	159
<i>MAOA</i> Monoamine oxidase A	0	0	7	1298
<i>DTNBP1</i> Dysbindin	2	251	1	293
<i>SLCA2</i> Norepinephrine transporter	3	520	0	0
<i>NR3C1</i> Glucocorticoid receptor	2	1063	1	98
<i>ACE</i> Angiotensin-converting enzyme	1	313	1	35
<i>HTR6</i> Serotonin receptor 6	1	34	1	91
<i>PD1A, PDE11A</i> Cyclic nucleotide phosphodiesterases	2	419	1	204

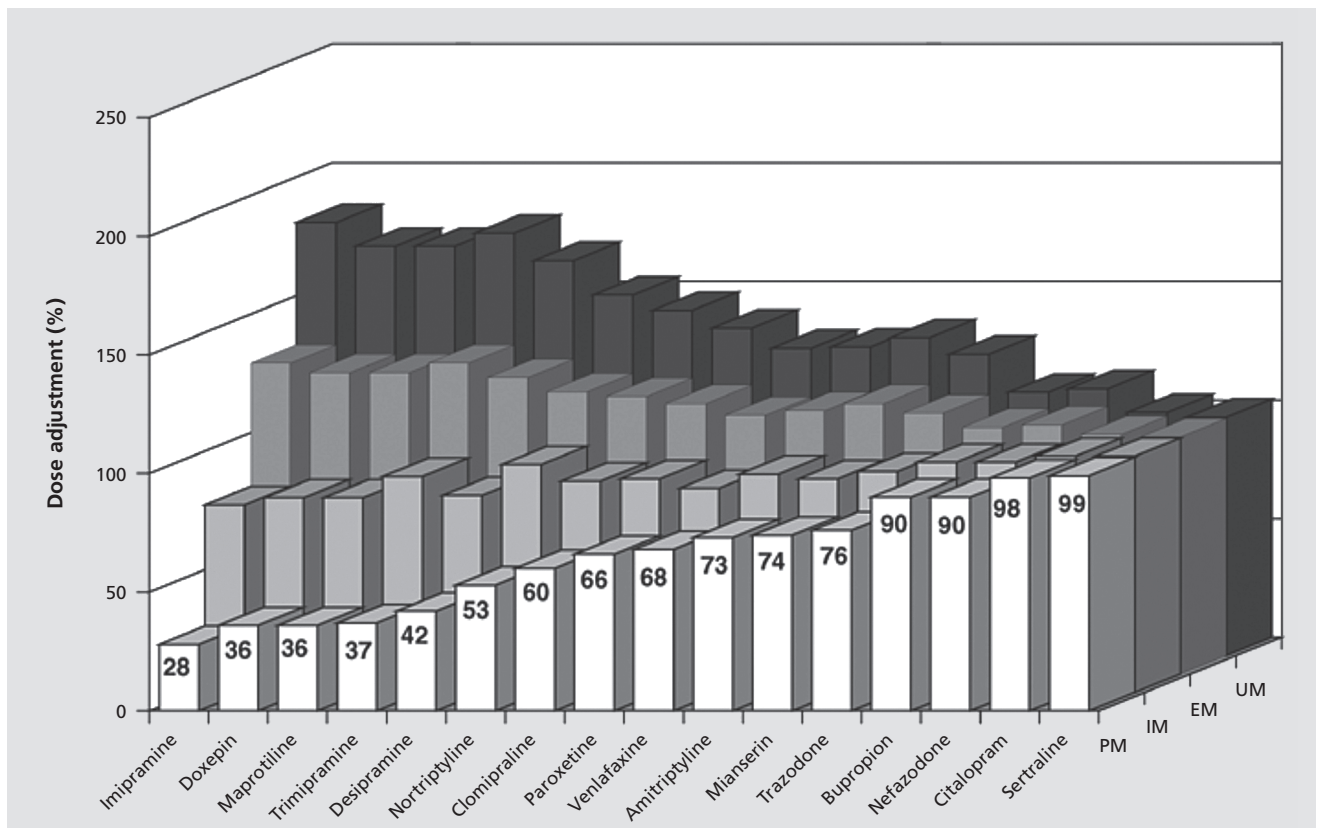
**Table II.** Summary of data survey by Horstmann and Binder.<sup>13</sup>

reason, Kirchheiner et al<sup>43</sup> made specific recommendations for dosage based on the effects of variants of the genes encoding those enzymes on bioavailability of several widely used antidepressants. The recommended dose adjustments based on CYP2D6 function can be seen in *Figure 1*; the dose adjustments based on CYP2C19 can be seen in *Figure 2*.

There is a solid scientific foundation for the recommendations made Kirchheiner and colleagues, which indicate a readiness for clinical translation in this area. Other groups have, however, questioned whether we are indeed ready to use in routine clinical care the testing for CYP450 polymorphisms in adults with nonpsychotic depression treated with SSRIs. The Evaluation of

Genomic Applications in Practice and Prevention (EGAPP) Working Group, supported by the Centers for Disease Control and Prevention (CDC), found insufficient evidence for a recommendation regarding the use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression. The EGAPP summarized its recommendations as follows: "In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed." This recommendation was based on the following rationale:

The EGAPP Working Group found no evidence linking testing for CYP450 to clinical outcomes in adults treated



**Figure 1.** CYP2D6-mediated quantitative influences on pharmacokinetics of antidepressant drugs expressed as percent dose adjustments: CYP2D6 poor metabolizers (PM, white), intermediate metabolizers (IM, gray), extensive metabolizers (EM, dark gray), ultrarapid metabolizers (UM, black). Dose adjustments were calculated according to the data given in *Table II*. If data on active drug moiety (consisting on active principle metabolite+parent drug of active enantiomers of a racemic drug) were given, dose recommendations were based on these data only (other studies not providing so detailed information were not incorporated). If more than one study was integrated, the weighted mean for the dose adjustment was taken according to the number of poor metabolizers in each study. Data on mirtazapine, moclobemide, fluoxetine, and maprotiline were not shown in the figure, since no dose adjustment based on CYP2D6 can be recommended at present.

Reproduced from ref 43: Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry*. 2004;9:442-473. Copyright © Nature Publishing Group 2004

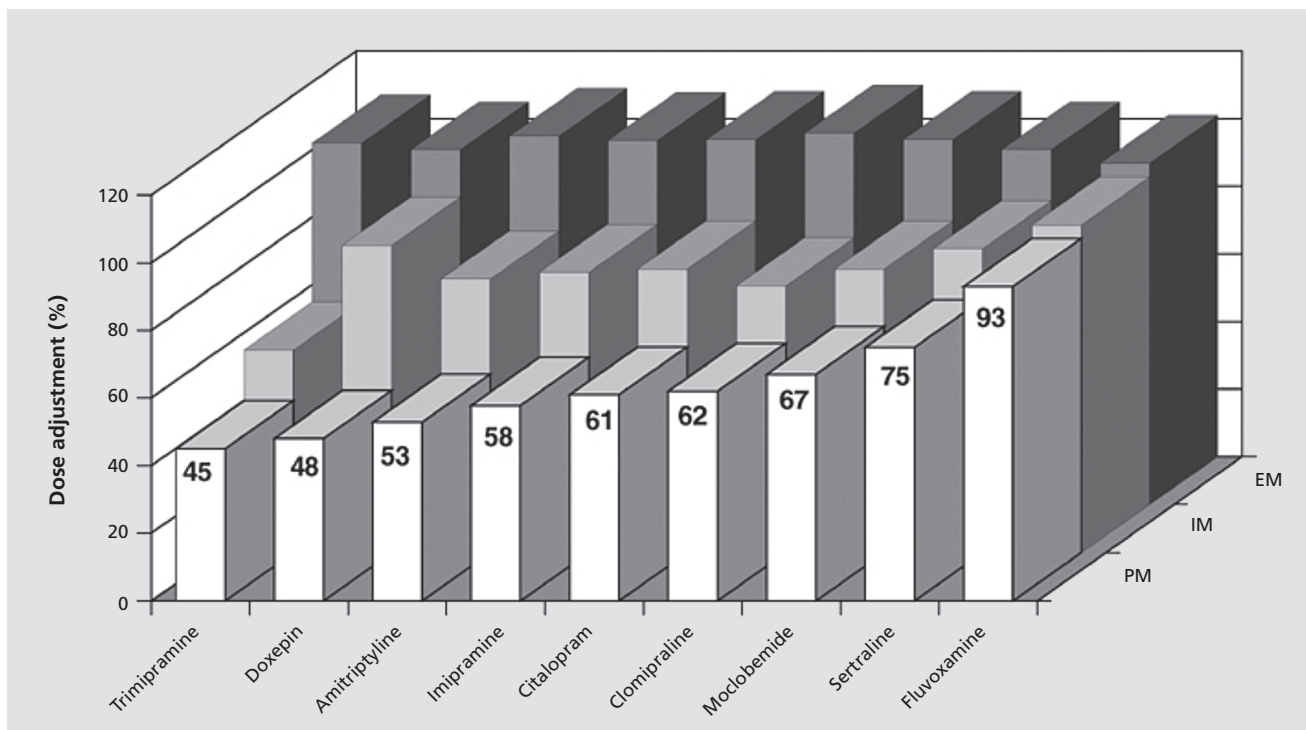
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with SSRIs. While some studies of a single SSRI dose in healthy patients report an association between genotypic CYP450 drug metabolizer status and circulating SSRI levels, this association was not supported by studies of patients receiving ongoing SSRI treatment. Further, CYP450 genotypes are not consistently associated with the patient outcomes of interest, including clinical response to SSRI treatment or adverse events as a result of treatment. No evidence was available showing that the results of CYP450 testing influenced SSRI choice or dose and improved patient outcomes, or was useful in medical, personal, or public health decision-making. In the absence of evidence supporting clinical utility, it is not known if potential benefits from CYP450 testing will outweigh potential harms. Potential harms may include increased cost without impact on clinical decision making or improvement in patient outcomes, less effective treatment with SSRI drugs, or inappropriate use of genotype information in the management of other drugs metabolized by CYP450 enzymes.<sup>44</sup>

The major issue in the domain of pharmacokinetics is not whether the CYP450 genes have a role in the metab-

olism of antidepressants, which they do, but if sufficiently solid evidence exists that justify the benefits of genetic testing for them routinely in the clinic. For those benefits to be documented, the EGAPP Working Group recommends “adequately powered, randomized controlled clinical trials that compare patient outcomes when treatment is informed by genotyping tests versus empirical treatment. Because depression is prevalent and is an important public health issue, and because SSRIs are widely prescribed, such trials are feasible and essential to determine best management practices with respect to CYP450 testing.”

It is, however, challenging to obtain competitive funding for such studies. The conundrum here is that, while such studies are critically needed for translation of research to practice to occur, they are not designed to test a conceptually novel hypothesis. Work that is not hypothesis-driven tends not to fare well in the fierce competition for research funds, which is only getting worse.<sup>45</sup> In our opinion it is unlikely that the necessary funding, which is required for large, definitive translational treatment stud-



**Figure 2.** CYP2C19-mediated quantitative influences on pharmacokinetics of antidepressant drugs expressed as percentage dose adaptations: CYP2C19 poor metabolizers (PM, white), intermediate metabolizers (IM, gray), extensive metabolizers (EM, dark gray).

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ies, will be allocated to this type of research in the foreseeable future. , unless a concerted effort is made to fund studies that are required to accelerate the translational pathway from medical knowledge to clinical practice. We are hopeful that such studies might fall under the domain of the recently proposed - and much needed - National Center for Advancing Translational Sciences (NCATS).<sup>46</sup>

## Conclusions

The gap from research to translation is still vast in the area of pharmacogenomics of antidepressants, in spite of over a decade of intensive work.<sup>47-55</sup> Two major steps need to occur before depressed patients can benefit from genomic tools for the optimization of their treatment. The first is that existing research findings need to be further solidified, and current controversies and disparate results must be understood and integrated into a universally accepted body of knowledge. That is what the field is currently dealing with in the domain of pharmacodynamics—or drug effects. The second step is in the area of bringing accepted research findings into practice. The issue in this domain is not whether there is solid scientific evidence; it is in the realm of cost-benefit: will genetic testing, even though logical and rational, be indeed clinically

beneficial so that it ought to become part of routine clinical care? This is the locus of the translational gap in the domain of pharmacokinetics. Overall, pursuit of a scientific basis to choose a specific drug, maximizing therapeutic effects and minimizing ADRs, is so important that the pharmacogenomics of depression has become a burgeoning area of research. Depression, for which we have no biological predictors of drug response, is a key target for advancement in the field of pharmacogenomics, which has been identified by the NIH Director Francis Collins as one of the key areas of national research priority.<sup>56</sup> We are cautiously hopeful that in the current decade much progress will be achieved in developing and implementing pharmacogenomics as a translational clinical tool to improve the outcomes and reduce the risks of antidepressant treatment. Furthermore, novel and robust pharmacogenomic findings would represent the next logical therapeutic targets for drug development in depression. As examples, recent work by our group has identified phosphodiesterases (PDE11A) and inflammatory mediators (PSMB4, TBX21, and STAT3) as potential novel antidepressant targets.<sup>3,54</sup> This way, pharmacogenomics will not only identify predictors of response to existing treatments, it will also have the potential to lead to conceptually novel treatments. □

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## Farmacogenómica de la depresión: una evaluación crítica

Han sido considerables las promesas y esperanzas respecto a que la farmacogenómica pudiera optimizar los tratamientos existentes para la depresión mayor, así como identificar nuevos blancos para el descubrimiento de fármacos. Inmediatamente después de la secuenciación del genoma humano hubo grandes esperanzas en que rápidamente se alcanzaría un tremendo progreso en la farmacogenómica. En los últimos diez años este entusiasmo inicial fue reemplazado por un prudente optimismo y se ha recorrido un largo camino hacia el objetivo de guiar la terapéutica en base a la genómica. Así como se sigue progresando en el esfuerzo por traducir los descubrimientos en aplicaciones clínicas sigue progresando y actualmente se cuenta con un gran conjunto de conocimientos así como una clara dirección a futuro. Este artículo entregará una evaluación crítica del estado del arte en la farmacogenómica de la depresión, tanto en términos farmacodinámicos como farmacocinéticos.

## Pharmacogénomique de la dépression : une évaluation critique

La pharmacogénomique a soulevé promesses et espoirs considérables d'optimiser les traitements existants de la dépression majeure et de trouver de nouvelles cibles pour la recherche pharmaceutique. Le séquençage du génome humain a été immédiatement suivi d'espoirs sans précédents de progrès rapides en pharmacogénomique. Cet enthousiasme a été remplacé ces 10 dernières années par un optimisme modéré, bien que nous ayons parcouru un long chemin vers les recommandations thérapeutiques basées sur la génomique. La traduction des découvertes en applications cliniques est en cours et nous disposons maintenant de connaissances élargies et de perspectives claires. Cet article propose une évaluation critique de l'état de l'art sur la pharmacogénomique de la dépression, à la fois en termes de pharmacodynamique et de pharmacocinétique.

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