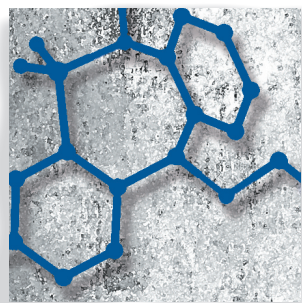


## *Prediction of individual response to antidepressants and antipsychotics: an integrated concept*

Sheldon H. Preskorn, MD



### Introduction

Every day, clinicians face the challenge of trying to predict the effectiveness (ie, efficacy balanced against safety/tolerability) of antidepressants and antipsychotics in individual patients. There are two main limitations to making such predictions. First, there are many unknown sources of variability. Second, there are many known sources of variability—both inherited and

*In both clinical trials and daily practice, there can be substantial inter- and even intraindividual variability in response—whether beneficial or adverse—to antidepressants and antipsychotic medications. So far, no tools have become available to predict the outcome of these treatments in specific patients. This is because the causes of such variability are often not known, and when they are, there is no way of predicting the effects of their various potential combinations in an individual. Given this background, this paper presents a conceptual framework for understanding known factors and their combinations so that eventually clinicians can better predict what medication(s) to select and at what dose they can optimize the outcome for a given individual. This framework is flexible enough to be readily adaptable as new information becomes available. The causes of variation in patient response are grouped into four categories: (i) genetics; (ii) age; (iii) disease; and (iv) environment (internal). Four cases of increasing complexity are used to illustrate the applicability of this framework in a clinically relevant way. In addition, this paper reviews tools that the clinician can use to assess for and quantify such inter- and intraindividual variability. With the information gained, treatment can be adjusted to compensate for such variability, in order to optimize outcome. Finally, the limitations of existing antidepressant and antipsychotic therapy and the way they reduce current ability to predict response is discussed.*

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acquired—which interact in complex ways. There is no comprehensive way to take all of this information into account at the point of care to allow a clinician to efficiently select the best drug, or set of drugs, for his or her patient. This paper discusses these issues based on the relevant literature, and presents clinical cases to illustrate specific points from a “big picture” perspective. More specific sources of variability in patient response will be discussed elsewhere in this issue. This paper will provide a conceptual framework to aid understanding of the sources of such variability and the tools that are available to the clinician to assess it (eg, therapeutic drug monitoring for pharmacokinetic variance) and guide treatment adjustment (eg, dose reduction in a “poor” metabolizer).

## Limitations of knowledge and treatments

Psychiatric diagnoses and nosology—certainly in the area of affective and psychotic illnesses—remain at the level of syndromic diagnoses (ie, clusters based on signs and symptoms) rather than at the level of either pathophysiology or pathoetiology.<sup>1</sup> Psychiatric nosology as codified in the *Diagnostic and Statistical Manual of Mental Disorders*, 5<sup>th</sup> edition (*DSM-5*) has not fundamentally changed, in terms of understanding, from *DSM-IV*, published a decade ago.<sup>2</sup> While some readers may know and accept the limitations which exist with current psychiatric nosology and the tremendous challenges and complexities involved in understanding the pathophysiologies and pathoetiologies underlying these syndromes, many probably do not.

The history of medicine teaches that syndromic diagnoses can rarely—if ever—be reduced to a single condition when understood from the perspective of pathophysiology and/or pathoetiology. Drugs work at the level of pathophysiology or pathoetiology, not at the level of syndromic diagnoses. When pathophysiology and pathoetiology are known, then rational drug discovery can be based on biologically relevant targets. Given this framework, consider the strides that have been made in the development of drugs aimed at stopping the replication of the human immunodeficiency virus to prevent the development of AIDS,<sup>3</sup> and contrast that with the last 60 years of antidepressant and antipsychotic drug development, which has mainly been devoted to refining the pharmacology of chlorpromazine and its derivatives, which include imipramine, the

first tricyclic antidepressant. While these development efforts have greatly increased the safety and tolerability of subsequent drugs, particularly for antidepressants, they have not changed the mechanisms of action believed to underlie their antidepressant and antipsychotic efficacy. In the case of antipsychotics, all existing antipsychotics, with the exception of clozapine, treat only one component of the schizophrenia syndrome: the positive symptoms (ie, hallucinations, delusion, and thought disorder) and have little to no effect on negative symptoms (eg, anhedonia, amotivation, and lack of social competence) or the cognitive impairment associated with schizophrenia. That is part of the reason that “remission” in schizophrenia is commonly defined as a 20% percent reduction in the Positive and Negative Symptoms of Schizophrenia Scale. In reality, this falls pathetically short of a true “remission” of this devastating illness.

The antipsychotic efficacy of these drugs is believed to be based on their ability to block dopamine D2 receptors. Since the serendipitous discovery of the antipsychotic efficacy of chlorpromazine, new antipsychotic drug discovery over the last 50 years has mainly been based on tweaking the structure of the phenothiazine and subsequent molecules (eg, haloperidol) to eliminate undesired mechanisms of action (eg, muscarinic receptor blockade) and thus improve tolerability. The process has gone full circle, from drugs with multiple mechanisms of action (eg, chlorpromazine, which parathetically meets most of the criteria for “atypicality”) to drugs that are essentially selective D2 receptor full antagonists (eg, haloperidol) to newer antipsychotics with multiple mechanisms of action (eg, olanzapine) and most recently to selective partial D2 agonists (eg, aripiprazole). Nevertheless, all of these drugs have the same fundamental mechanism of action, which is D2 receptor antagonism.

The fact that the essential mechanism of action does not differ between the different antipsychotics might explain why they have comparable efficacy, and why patients who do not respond to one often do not respond to others. The exception remains clozapine. To date, despite decades of work, we have only a general understanding of its efficacy in individuals with otherwise treatment-resistant schizophrenia (ie, that it influences—mostly antagonizes—a great number of different neurotransmitter systems). The results of the largest treatment study of schizophrenia, the National Institute

of Mental Health (NIMH)-funded Clinical Antipsychotic Treatment Intervention Effectiveness (CATIE) trial, underscore the limited efficacy of current antipsychotics.<sup>4</sup> At present, there are few explanations as to why given patients do or do not respond to specific antipsychotics.

The situation with antidepressants is much the same. All current antidepressants appear to work via effects on one or more biogenic amine neurotransmitter systems. This might be the reason for their substantially overlapping spectrum of antidepressant efficacy based on the NIMH-funded, largest treatment trial in major depressive disorder, the Sequential Treatment Alternatives to Relieve Depression (STAR\*D) trial. The bottom line of that study was that after four sequential adequate trials of virtually all existing antidepressants, 45% of patients with major depression remained significantly ill and not in remission. Moreover, the chance of responding to a subsequent trial of another biogenic amine-based antidepressant dropped considerably after the first failed trial, to approximately 10% after the third trial.<sup>5</sup>

Recently, there has been encouraging results with a series of glutaminergic drugs (eg, ketamine) suggesting that perhaps 60% of patients with depressive illness not responsive to biogenic amine antidepressants may respond to glutaminergic antidepressants, based on the author's clinical trial experience with such agents. If this experience is borne out by future studies, it suggests that there are at least three forms of depressive illnesses: (i) those responsive to biogenic amine antidepressants; (ii) those responsive to glutaminergic but not biogenic amine antidepressants; and (iii) those not responsive to either. Such a division of patients into groups according to their clinical response to antidepressants might be helpful in terms of further exploring the differences in the pathophysiology of the different forms of depressive illness while simultaneously addressing a currently poorly understood source of variance in antidepressant response.<sup>6</sup> Of course, there are likely to be more than these three forms of depressive illnesses, such as those caused not by "neurotransmitter imbalances" but instead by inflammatory processes, for example.<sup>7</sup> The point is to begin to divide a rather amorphous syndromic diagnosis into biologically meaningful subtypes.

The above discussion provides a possible explanation for the current signal-to-noise problem in trying

to predict antidepressant and antipsychotic efficacy. In clinical trials of these agents, approximately one third of patients respond to placebo treatment, one third respond specifically to the drug (ie, overall drug response minus response to placebo) and one third do not respond, translating into a signal-to-noise ratio of 1:2. That ratio simultaneously underscores the serious need to be able to predict efficacy to a given treatment and the difficulty of trying to discover reliable and valid predictors.

### Understanding variability in drug response

Next, this review will present a way of conceptualizing the source of variance in patients who have a form of depressive and/or psychotic illness which is generally responsive to existing medications.

Most drugs—and certainly all current antidepressants and antipsychotics—work by affecting proteins which are important mediators of human physiology. There are four major categories of such proteins: transporters, enzymes, receptors, and ion channels. By binding to these targets, drugs are capable of changing their conformational structure and hence their function, which is how they treat disease.

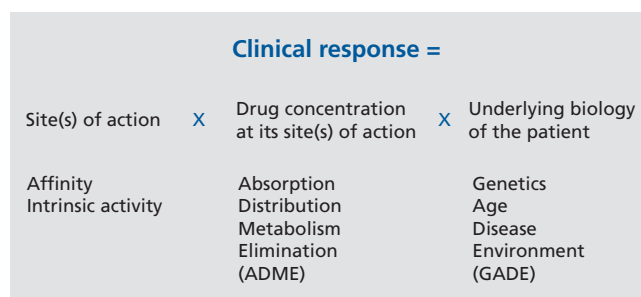
Transporters and enzymes not only mediate the pharmacodynamics of drugs, but also mediate their pharmacokinetics. Transporters are involved in their absorption, distribution, and elimination while enzymes are involved in the biotransformation of drugs into more polar metabolites as a necessary step in their eventual elimination from the body.

Since proteins are gene products, variants in the coding genes (ie, polymorphisms) can result in variants in the proteins and their function ranging from inconsequential to substantial. For example, variants in the gene coding for CYP2D6 (a member of the cytochrome P450 family of enzymes) can result in nonfunctional enzyme (CYP2D6 poor metabolizers or PMs), or reduced activity (CYP2D6 intermediate metabolizers or IMs) when compared with the normal or "wild-type" gene (CYP2D6 extensive metabolizers or EMs). On the other hand, multiple copies of the gene can result in increased enzymatic capacity (CYP2D6 ultrarapid metabolizers or UMs).

The above factors are summarized in the equation in *Figure 1*.<sup>8</sup> The first variable in this equation, pharmacodynamics, is defined as the mode of action at the

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molecular level (ie, the site[s] to which the drug binds to produce its effect[s]). A drug may affect one or more site(s) of action. Its highest affinity site of action may mediate either a desired or an undesired effect. Depending on the relative binding affinity of the drug, it may be selective for a given target (ie, substantially affect it, but no other sites, to a clinically meaningful degree at its lowest concentration) or may affect multiple sites at virtually the same concentration. The serotonin selective reuptake inhibitors (SSRIs) are an example of the former type of drug, whereas the “atypical” antipsychotics are examples of the latter type of drug. Parenthetically, “atypical” is in quotation marks because the term has commonly been used to designate antipsychotics marketed since 1990; however, chlorpromazine meets most of the criteria for “atypicality” and hence this “atypical” pharmacology is not new. Drugs that work on receptors can be separated into three principal categories: (i) agonists that stimulate the biological functions tied to the receptor that they bind to; (ii) antagonists that block the effect of the endogenous (or exogenous) agonists; and (iii) inverse agonists that have an effect on their target (eg, an ion channel) opposite to that of an agonist. Between these three distinct classes are drugs which are partial agonists and partial inverse agonists. Most drugs, including most antidepressants and antipsychotics, are antagonist of the receptors or transporters that they bind to. Exceptions are agomelatine which is an agonist at the melatonin receptors, MT1 and MT2, and an antagonist at the 5-HT (serotonin) 2C receptor and aripiprazole which is a partial agonist at the D2 receptor. Genetic polymorphisms of receptors or transporters can alter the sensitivity of patients to the effects of drugs.



**Figure 1.** Three variables that determine drug effect (ie, clinical response).

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The second variable in the above equation, pharmacokinetics, is defined by four processes: absorption, distribution, metabolism, and elimination of the drug. Simplistically, pharmacodynamics can be considered as “what the drug does to the body” and pharmacokinetics as “what the body does to the drug.” The major clinically relevant pharmacokinetic variable for most drugs—at least based on our current knowledge—is the drug’s clearance (which is determined principally by its metabolism and elimination). Dosing rate (eg, mg/day) and clearance determine the concentration of the drug at the target under steady-state conditions. Virtually all—if not all—current antidepressants and antipsychotics over their recommended dosing range display linear pharmacokinetics (ie, doubling the dose doubles its concentration). If clearance is halved (eg, the coadministration of an inhibitor of the enzyme principally responsible for the metabolism of the drug), the concentration will double. Knowing that the clearance of antidepressants and antipsychotics can vary by a factor of two to three times or more from one patient to another explains why finding the ideal dose to produce the ideal concentration can be problematic. In principle, the drug concentration in circulating plasma or serum is in equilibrium with the concentration at other body sites such as at the receptor, transporter, enzyme, or ion channel at the synapse of interest. Recently, however, this pharmacological dogma has been challenged by the discovery of drug transporters.<sup>9</sup>

With the above caveat, the most biologically relevant concentration (ie, at the site of action in the synapse of interest) is not readily measured—certainly not in routine clinical practice. Instead, the concentration of the drug in plasma or serum is used as a surrogate clinically. This practice is called therapeutic drug monitoring (TDM) and is based on the aforementioned concept of equilibrium between the concentration in plasma/serum and the concentration of the drug at its site of action.

Drugs may be metabolized to either active and/or inactive metabolites. These active metabolites may have a pharmacological profile quite similar to the administered drug (eg, paliperidone and risperidone) or quite different (eg, terfenadine versus fexofenadine, as discussed later in this paper).

The third variable in this equation is the biological variability amongst patients, which can make specific patients either sensitive or resistant to specific effects of a given drug at a given dose or plasma concentration.

So far, the discussion of the third variable has only considered genetic variability. However, there are at least three other sources: age, disease, and the internal environment. The clinical adage of “start low and go slow” in the elderly is a reflection of the fact that as patients age they frequently become sensitive to the effects of specific drugs. That may be mediated by changes in either pharmacodynamics and/or pharmacokinetics. Age may simply be a surrogate for the cumulative effects of time-associated decline in organ function, particularly the liver and the kidneys, for virtually all drugs, and the brain in particular for drugs that affect the central nervous system (CNS). However, age as a variable can go beyond simply advanced age. Some genes are expressed more or less at specific age. For example, cytochrome P450 3A3/4 is inducible by testosterone (T) and estrogen (E): T>E such that its activity increases after puberty and decreases in senescence, and is generally higher in activity in males than in females.

Disease can affect the organs responsible for the clearance of drugs such as liver, kidney, and heart because left ventricular stroke volume determines renal and hepatic blood flow, which in turn determines hepatic and renal clearance. That is a pharmacokinetic effect.

However, disease can also affect end-organ response (ie, pharmacodynamics). For example, Parkinson’s disease and Alzheimer’s disease can shift the dose and concentration response curves for the adverse effects of D2 and muscarine (M) and acetylcholine receptor antagonists, respectively, because these illnesses diminish the individual’s ability to compensate for the blockade of these receptors.

Another source of variance (ie, the fourth category under the third variable in the above equation) are state-dependent changes in the internal milieu of a given individual’s body due to factors such as diet (dishes rich in smoked or charcoal-grilled food), substance use (eg, smoking and alcohol in moderate or excessive amounts), and the ingestion of medications, including steroids.

By way of example, smoking and a diet rich in smoked and charcoal-grilled foods can induce the production of enzymes such as CYP 1A2 and increase the clearance of drugs which are substantially dependent on this enzyme for their clearance. Examples of such drugs include certain antipsychotics (eg, clozapine and its derivative, olanzapine) and antidepressants (eg, duloxetine and fluvoxamine). Of note, a higher percent-

age of individuals with affective and psychotic disorders smoke compared with the general population. Indeed, 80% of patients with schizophrenia smoke.<sup>10</sup> The effects of smoking as well as other inducers are quite variable, and may be due in part to variations in the promoter region of the gene.

The effects of alcohol on the pharmacokinetics of specific drugs is triphasic. Acute ingestion of a large quantity of alcohol increases the bioavailability of some drugs by inhibiting their first-pass oxidative metabolism during its absorption in the small bowel as well as by inhibiting the effect of efflux transporters. On the other hand, chronic ingestion of moderate amounts of alcohol can induce oxidative drug metabolism, leading to increased clearance of some drugs. Finally, long-term alcoholism can cause cirrhosis, leading to the increased accumulation of specific drugs. There is actually a substantial genetic predisposition to alcoholism such that there can be a complex interplay between genes increasing risk for having alcoholism and the effects of the alcoholism on drug effects.

The pharmacodynamics and/or pharmacokinetics of a specific drug can be profoundly affected by the coadministration of other drugs (ie, drug-drug interactions). There can also be complex drug-gene interactions. Studies on CYP2D6 illustrates these points as follows: fluoxetine and paroxetine are two antidepressants which are capable of substantially inhibiting CYP2D6 at their usual antidepressant doses. The degree of inhibition is a function of the concentration of the inhibitor. On average, 20 and 40 mg/day of either fluoxetine or paroxetine will convert 66% and 95% of genotypic CYP2D6 EMs into phenotypic CYP2D6 PMs.<sup>11</sup> However, genotypic CYP2D6 IM and UM patients are sensitive and resistant, respectively, to such phenoconversion induced by such drugs.<sup>12</sup>

### Complexity of prediction in clinical practice

As indicated by *Figure 1*, there are many factors that influence the response to a specific drug. It might be that the heritability of some of these factors are low (ie, that many nongenetic factors can play an important role). These nongenetic factors also explain why there can be important intraindividual variation in drug response. This author suspects that the interindividual variability amongst patients and intraindividual variation within the same patient (because it is a state phenomenon) produced by nongenetic factors such as what medica-

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tions (drugs) the individuals is taking is likely greater than interindividual variability produced by genetics.

Among the nongenetic factors, multiple medication use (MMU) plays a significant role in determining drug response. Moreover, MMU is frequent and highly variable from one individual to another. For example, 60% of the general American and Canadian population, 65 years or older, take five or more prescription drugs.<sup>13,14</sup> “General population” here refers to all Americans and Canadians, irrespective of their health care status.

Given the number of prescription drugs currently on the market, over 520 quadrillion different five-drug combinations could theoretically be given to a patient.<sup>15,16</sup> This is the figure arrived at when five-drug combinations are used as an example; obviously a different number of possible combinations would result from a different number of drugs. Regardless, a patient could be on an enormous number of combinations of medications. This is important because it translates into the number of variations of human biology that can be produced by the medications that the patient is taking. Recall that all drugs except anti-infectives treat disease by altering human biology. The point is that a prescriber or groups of prescribers can produce enormous variations in human biology as a result of the drugs they prescribe for a patient. That variation is in addition to that due to the individual’s genetics, age, concurrent diseases, or other individual factors such as social habits and diet.

Of relevance to this article, MMU is more frequent and more complex in individuals with affective and psychotic disorders than it is in a nonpsychiatric population.<sup>17,18</sup> For example, a recent survey found that 785 of 900 patients being treated with an antidepressant in routine clinical practice were on at least one other medication in addition to their antidepressant (median and mean numbers of drugs being taken were 3 and 4 inclusive of their antidepressant, respectively, with the range being 0 to 22).<sup>12</sup> While 4% of this population were genotypically CYP2D6 PMs, 28% were phenotypically CYP2D6 PMs due to concomitant administration of one or more drugs capable of inhibiting CYP2D6.

For these reasons, all four sources of variance (both state and trait) listed under variable 3 must be considered when attempting to understand and/or predict a given patient’s sensitivity or resistance to either beneficial or adverse effects of a given drug at a given moment in treatment.

## Case illustrations

Four cases will be presented to illustrate the sources of variation in drug effect. The first three cases can be explained by the results of formal studies which will be described. The fourth case can be explained by well-established principles of physiology and pharmacology.

### **Case 1: How a gene can determine the efficacy of an antidepressant**

This 40-year-old man suffered from a major depressive episode and was treated with venlafaxine titrated up to 300 mg/day. Despite an adequate trial in terms of dose, duration and adherence, he experienced no benefit. He was genotyped and found to be a CYP2D6 PM.

#### *Discussion*

This case example can be explained by the recently published results of a formal reanalysis of four studies—essentially identical in terms of design and methodology—conducted and submitted to the US Food and Drug Administration in the mid 1990s to support the registration of venlafaxine.<sup>19</sup> These four studies were specifically selected for reanalysis because a plasma sample was obtained during each study to measure the levels of venlafaxine and O-desmethylvenlafaxine (desvenlafaxine). The reason for the reanalysis was because the ratio of desvenlafaxine to venlafaxine was subsequently established as a way of phenotyping CYP2D6 EMs versus PMs.<sup>20</sup> Thus, the availability of these plasma levels permitted reanalysis by dividing those who received venlafaxine into two groups—those who were phenotypically CYP2D6 EMs versus CYP2D6 PMs—and then comparing their responses with each other and with the placebo group. Parenthetically, the concomitant medication that these subjects received for a month before and throughout the study was collected at the time that these studies were performed. This data was examined as part of the reanalysis and none of these study participants were on medications known to inhibit CYP2D6. Hence phenotypic conversion from CYP2D6 EM to PM status was unlikely to have affected the results. The results showed that specific response and remission rates with venlafaxine (ie, rates on drug minus the rate on the parallel placebo group) were 2.5 to 3 times higher in EMs versus PMs ( $P < 0.01$ ). In ad-

dition, the response and remission rates in EMs were statistically greater than on placebo. In contrast, the response and remissions rates in PMs treated with venlafaxine did not differ from those produced by placebo.

The reason underlying these findings was not established by this reanalysis. There are at least two possible explanations: (i) CYP2D6 PMs are not responsive to antidepressants that have a biogenic amine mechanism of action; or (ii) venlafaxine has to be converted into desvenlafaxine to be active. This study made the observation but did not establish the cause. Nevertheless, this finding is the largest genetically determined difference in antidepressant efficacy reported to date, to the author's knowledge.

A large-scale, multisite, randomized prospective study is currently under way to determine if antidepressant outcome can be predicted by taking this finding along with others into account when selecting an antidepressant for a patient.

### **Case 2: How an environmental factor can produce the same outcome as a genetic difference**

This 45-year-old woman was on maintenance treatment with tamoxifen following surgical resection of an estrogen/progesterone receptor-positive breast cancer 2 years earlier, and was also being treated with paroxetine, 40 mg/day, for recurrent major depressive disorder. Despite the tamoxifen, this patient had a recurrence of her breast cancer and subsequently died from it.

#### *Discussion*

Several facts are relevant to this clinical case. First, tamoxifen is a prodrug that must be converted to its active metabolite, endoxifen, to be active against breast cancer. This conversion is dependent on CYP2D6-mediated oxidative drug metabolism.<sup>21</sup> That finding led to a pharmacoepidemiology study showing that genotypic CYP2D6 PMs had a greater likelihood of tamoxifen failure in terms of both time to tumor recurrence and time to death (ie, a shorter survival curve).<sup>22</sup> The recognition that paroxetine could cause phenoconversion to CYP2D6 PM status as described above led to another pharmacoepidemiology study that showed that concomitant administration of paroxetine with tamoxifen increased the likelihood of tamoxifen failure and a shorter survival time.<sup>23</sup> In this case, it is irrelevant as

to whether this patient was genetically a CYP2D6 PM, because the dose of paroxetine she was taking was sufficient to convert virtually all CYP2D6 EMs and IMs into a phenotypic CYP2D6 PM. This case illustrates why multiple medication use must be taken into account when endeavoring to predict treatment outcome, and that a psychiatric drug can be the cause of poor outcome with nonpsychiatric treatment. Parenthetically, patients such as this woman are at increased likelihood of being on an antidepressant like paroxetine because these medications are used to treat "hot flashes" as well as depressive illnesses.

The case of this woman occurred before it was known that tamoxifen was a prodrug and had to be converted by CYP2D6 to the active agent, endoxifen. For this reason, the treating physician neither knew nor should have known, and thus it did not represent a medical error. Now, these facts are known. That is the reason why the package insert for tamoxifen has been revised to include these facts, why software packages for drug-drug and gene-drug interactions contain such warnings, and why physicians are taught about these matters to avoid untoward outcomes and the potential liabilities that come with them.

### **Case 3: How multiple genetic, environmental, and disease factors can interact to modify drug response**

A 66-year-old Caucasian man with psychotic major depression had been successfully treated with paroxetine, 40 mg/day, and iloperidone, 24 mg/day administered once a day, and was in the maintenance phase of therapy. He developed bronchitis and his internist treated him with clarithromycin, 250 mg twice daily for 14 days. At the end of the first week of antibiotic treatment, he attended his routine psychiatric follow-up. He was doing well except for a couple of recent episodes of intermittent dizziness and one episode of near fainting. His comorbid medical conditions included type 2 diabetes mellitus, which was well controlled with metformin, morbid obesity, and quadruple coronary bypass surgery 4 years earlier.

#### *Discussion*

Based on the equation in *Figure 1* and knowledge of the pharmacology of iloperidone, this individual can be predicted to be at risk for a fatal arrhythmia known as

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torsades de pointes (TdP). In fact, that is likely cause of his near-syncopal episode. This diagnosis can be confirmed in the office doing an electrocardiogram to measure the duration of the patient's QTc interval.

This case can be explained in large part by the results of what the FDA terms a "thorough QTc" (TQT) study. These studies are done to assess the risk of clinically meaningful QTc prolongation due to medication (in this case, iloperidone).<sup>24</sup> This study was conducted in accordance with FDA guidance for such studies. The design included: (i) random assignment to one of three doses of iloperidone or placebo or one of two active control (ie, quetiapine and ziprasidone); (ii) a supra-therapeutic dose of iloperidone (ie, 24 mg once a day); and (iii) treatment first with the iloperidone alone, then with CYP2D6 inhibition alone (ie, the addition of paroxetine) and then in combination with CYP 3A4 inhibition as a result of the addition of ketoconazole (ie, combined treatment with iloperidone, paroxetine, and ketoconazole). Finally, genotyping was done on all participants in the study for specific candidate genes: CYP2D6 and voltage-gated potassium channel KCNQ gene because variants of this gene can predispose to drug acquired long QT interval syndrome including TdP.

A prolongation of the QTc by more than 60 milliseconds is considered by the FDA to be a clinically meaningful change indicating a risk for drug-induced TdP. There were 10 individuals in this TQT study who experienced such a prolongation. Six variables accounted for all 10 individuals: (i) being on iloperidone; (ii) being on the 24 mg/day schedule; (iii) concomitant paroxetine administration; (iv) concomitant ketoconazole administration; (v) variants of CYP2D6 conveying PM status; and (vi) variants of KCNQ gene conveying increased sensitivity to QT prolongation.<sup>25</sup> No single individual had all six variables. Instead, the presence of only two or three of these variables in different combinations was sufficient. In other words, the same adverse event could be due to several different combinations of causes including both state and trait variables.

This case thus builds on the previous two cases to illustrate the complexity of predicting the outcome of antidepressant and antipsychotic treatment. This patient could have had an uneventful outcome if his dose of iloperidone had been kept sufficiently low but he may also have had no beneficial response for the same reason.

## **Case 4: How a drug formulation change and the physiological state of a patient explain a serious adverse event**

An 18-year-old high school student was treated with an SSRI and quetiapine 300 mg/day plus a benzodiazepine and diphenhydramine over a 2-week period. He had experienced nausea with decreased food and fluid intake and had lost 3 kg over the past 7 days. Over the same period of time, he experienced a drop in his blood pressure to 102/76 and an increase in heart rate to 92 bpm. Of note, he was a long-distance runner and his usual blood pressure and pulse rate were 120/60 and 55. His quetiapine was switched from the extended-release (ER) to the immediate-release (IR) formulation on the night his serious adverse effect occurred. He took his medications and correctly and went to sleep in a recliner in a semi-recumbent position. The next morning he was found unresponsive and was diagnosed with aspiration pneumonitis.

### *Discussion*

In this case, genetics to the best of current knowledge did not play a role in the adverse outcome, but several other factors did. These factors are as follows: (i) the dehydration which had already caused in decrease in his blood pressure and a compensatory increase in his heart rate; (ii) the switch from ER to IR quetiapine which resulted in a shorter time to maximum concentration and a 2.5 to 3.0 higher peak concentration of quetiapine and hence greater  $\alpha$ -1 receptor blockade; (iii) the semi-recumbent position which resulted in pooling of blood in his lower extremities as a result of  $\alpha$ -1 adrenergic receptor blockade produced by quetiapine; (iv) the combination of the sedative effects of the benzodiazepine (a  $\gamma$ -aminobutyric acid, GABA, agonist), and diphenhydramine and quetiapine (which are both H<sub>1</sub> histamine receptor antagonists); and finally (v) the likely impairment of his gag reflex by the dopamine D<sub>2</sub> receptor blockade, resulting from the higher quetiapine plasma, and hence brain, concentrations.

This case can be explained by well-established clinical knowledge and the clinical pharmacology of quetiapine as described in the package insert.

The major point of this case is how a change in the internal environment (dehydration) coupled with a change in the formulation of a product can make a profound impact on the outcome for an individual.



## Conclusion

The theme of this review is the notion that “personalized medicine” is more than just genetics. In fact, it requires the prescriber to take into account the physiological status of his or her patient at that moment in time, including his/her age, concomitant disease, and concomitant medications in addition to his/her genetics. This theme is not new: over 100 years ago, Claude Bernard (1813–1878) cautioned physicians to recognize that each patient is unique and that this uniqueness can vary over time. He used the term “idiosyncrasy” to describe this point-in-time uniqueness.

This paper has presented a way of organizing the knowledge about both interindividual and intraindividual variability affecting treatment outcome, and discussed four cases to illustrate these principles and concepts.

While genetics is not the only cause of variations in patient response, it has been, and will continue to be, a fruitful way of understanding an important source of such variability. Moreover, it is increasingly being used to

predict such variability so that clinicians can better prescribe the right drug at the right dose to a specific patient.

In line with these developments, there has been a concerted effort to keep health care providers and the general public aware of these developments through the dissemination of this knowledge. One such effort is the Clinical Pharmacogenetics Implementation Consortium (CPIC) which is a joint project between the Pharmacogenomics Knowledge Base (PharmGKB) and the Pharmacogenomics Research Network (PGRN).<sup>26</sup> The goal of this project is to expedite and support the implementation of pharmacogenomics research knowledge into clinical practice via changes in FDA labeling and making pharmacogenetic tests available to health care practitioners.<sup>27</sup>

Nonetheless, the prescriber using his/her judgment, knowledge, and experience, remains the critical element synthesizing all of the sources of interindividual and intraindividual variability in response. By monitoring the patient, the clinician can adjust treatment, even when the cause of the variability is yet not well understood. □

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# Pharmacological aspects

## **Predicción de la respuesta individual a antidepresivos y antipsicóticos: un concepto integrado**

Tanto en los ensayos clínicos como en la práctica diaria puede existir una importante variabilidad inter e incluso intraindividual en la respuesta a los efectos favorables o adversos de medicación antidepresiva y antipsicótica. Hasta ahora no se dispone de herramientas que puedan predecir el resultado de estos tratamientos en pacientes específicos. Esto es porque las causas de tal variabilidad a menudo son desconocidas, y cuando se conocen, no hay forma de predecir los efectos de sus varias combinaciones posibles para un sujeto. Teniendo en cuenta estos antecedentes, esta revisión presenta un marco conceptual para la comprensión de los factores conocidos y sus combinaciones para que los clínicos, eventualmente, puedan predecir mejor qué fármaco(s) seleccionar y en qué dosis, para optimizar el resultado para un sujeto determinado. Este marco es bastante flexible para ser fácilmente adaptable en la medida que se disponga de nueva información. Las causas de la variación en la respuesta del paciente se agrupan en cuatro categorías: a) genética, b) edad, c) enfermedad y d) ambiente (interno). Se emplean cuatro casos de complejidad creciente para ilustrar la aplicabilidad de este marco de una manera clínicamente relevante. Además este artículo revisa herramientas que el clínico puede emplear para evaluar y cuantificar variabilidad inter e intraindividual. Con la información obtenida el tratamiento puede ser ajustado para compensar tal variabilidad, con el fin de optimizar el resultado. Por último, se discuten las limitaciones de la terapia antidepresiva y antipsicótica existentes y la manera de reducir las posibilidades actuales de predicción de la respuesta.

## **Prédiction de la réponse individuelle aux antidépresseurs et aux antipsychotiques : un concept intégré.**

Que ce soit dans les études cliniques ou la pratique quotidienne, la variabilité des réponses inter- et même intra-individuelles (bénéfiques ou indésirables) aux traitements antidépresseurs et antipsychotiques peut être importante. Jusqu'à présent, nous ne disposons d'aucun outil pour prévoir les résultats de ces traitements chez des patients donnés, parce que les causes d'une telle variabilité sont souvent inconnues et quand elles le sont, il n'y a pas de moyen de prévoir les effets de leurs associations possibles chez une personne. Dans ce contexte, cet article présente un cadre conceptuel pour comprendre les facteurs connus et leurs associations afin que les médecins puissent finalement mieux prévoir quel(s) médicament(s) choisir et à quelle dose pour obtenir les meilleurs résultats chez une personne en particulier. Ce cadre est suffisamment flexible pour s'adapter facilement dès que des nouvelles données sont disponibles. Les causes de variation de la réponse des patients sont regroupées en quatre catégories : 1) génétique ; 2) âge ; 3) maladie ; 4) environnement (interne). Quatre cas de difficulté croissante illustrent la mise en pratique de ce cadre d'une façon cliniquement pertinente. De plus, cet article examine les outils que le médecin peut utiliser pour évaluer et quantifier la variabilité inter et intra-individuelle. Avec ces informations, le traitement peut être ajusté pour compenser une telle variabilité et optimiser le résultat. Enfin nous analysons les limites des traitements antidépresseurs et antipsychotiques existants et en quoi cela diminue la possibilité de prédire la réponse thérapeutique..

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