2-2009

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Accepted Manuscript

Title: The future (or lack of future) of personalized prescription in psychiatry

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Please cite this article as: de Leon J, The future (or lack of future) of personalized prescription in psychiatry, *Pharmacological Research* (2008), doi:10.1016/j.phrs.2008.10.002

Perspective

The future (or lack of future) of personalized prescription in psychiatry

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ABSTRACT

Rapid technological advances in genetics have created conceptual chaos regarding the genetics of drug response. Terms for differing concepts are used interchangeably: pharmacogenetics with pharmacogenomics, personalized medicine with personalized prescription. Biomarker has many definitions. The author prefers the concept of personalized prescription and uses it with implications beyond pharmacogenetics by considering all scientific information valid for prescribing medication. Genetics may not be crucial for all drugs. In this comprehensive view, clinicians must consider genetic, environmental and personal variables when prescribing medication and incorporate some basic pharmacological principles: 1) safety and efficacy, 2) pharmacokinetics and pharmacodynamics, 3) therapeutic window and prescriber's role, and 4) idiosyncratic and dose-related adverse drug reactions. Personalized prescription in the clinical environment can be expressed in two main ways: as personalized selection of the drug and as personalized dosing.

The future, or lack of future, of personalized drug selection and of personalized dosing in psychiatry is reviewed. Currently, the author thinks that, in psychiatry, pharmacogenetic tests have some potential in two areas: 1) excluding some drugs for some unusual patients (HLA-B*1502 genotyping in Asians for carbamazepine), and 2) using pharmacokinetic genes for personalizing dosing in narrow therapeutic window drugs. In the short term, there is dubious potential for other pharmacogenetic tests and no potential for pharmacogenetic testing to ascertain the best drug for each patient. Personalized dosing has immediate application if one understands it as the use of our current scientific knowledge of genetic, environmental and personal variables to determine dosing; its sole requirement is well-trained psychiatrists.

1. Introduction

The end of the 20th century brought new hopes of a revolution in medicine based on our advancing knowledge of the human genome [1,2]. Personalizing pharmacological treatment has been proposed as the driving force for implementing genetic advances in primary care [3,4]. The first pillar of the genetic or genomic revolution was the development of new technologies that permitted parallel genetic testing (testing for many genetic variations) by using computerized genotyping [5]. Currently, more advanced forms of these types of DNA microarray technologies [6], including the Illumina BeadArray platform [7], allow testing of more than one million single nucleotide polymorphisms (SNP) at a cost of less than $1,000 per sample, and the price is rapidly decreasing. The second pillar of this revolution was the mapping of the human genome which was completed in 2000 [8] and published in 2001 [9,10].

The first surprise stemming from the mapping of the human genome was that the human genome has only 30,000 genes (versus more than 100,000 expected) [11]. Nevertheless, 30,000 genes produce millions of genetic variations, including almost 9 million SNPs [12]. One would think that the reduction in the number of genes from the 100,000 expected to 30,000 found would simplify the task. However, it has become evident we do not yet know the function of approximately one third of human genes [13].

Recent developments have proven how naïve it was to think that the mapping of the human genome was going to change medicine in the short term. It is becoming clear that other types of genetic variations such as deletions or duplications, the so-called copy number variations (CNV), may have been neglected [14]. Unfortunately, many of the current platforms and systems used for genotyping pay attention mainly to SNPs and give little attention to CNVs. But CNVs may be important for pharmacogenomics [15]; it was a pharmacogenetic gene in which the clinical relevance of gene multiplications was discovered [16]. Less common genetic variations such as microsatellite polymorphisms and translocations, inversions, and substitutions may have some relevance in pharmacogenomics [17]. Finally, the relevance of epigenetics to pharmacogenetic response in humans is

not well understood [18], but it is important to know that a fly's drug tolerance to an anesthetic appeared to be mainly caused by epigenetic mechanisms [19].

The next four sections attempt to lessen the conceptual chaos that the rapid technological advances in genetics have created in the area of the genetics of drug response. The concepts of pharmacogenetics/pharmacogenomics, biomarkers, personalized medicine/personalized prescription are frequently used interchangeably but are not exactly the same in the author's view.

2. The concepts of pharmacogenetics and pharmacogenomics in the literature

Vogel [20] first coined the term pharmacogenetics, which for many years was associated with the genetics of pharmacokinetic factors, particularly of metabolic enzymes. In the 1990s, the concept of pharmacogenomics was also introduced in the literature. In 2001, Pirmohamed reported that pharmacogenetics had been defined as the study of variability in drug response, while the term pharmacogenomics was a broader term encompassing all genes in the genome that may determine drug response. He considered the distinction as arbitrary in that both terms were frequently used interchangeably [21]. The perspective of this author is that pharmacogenetics usually is used in the context of studies attempting to verify the influence of candidate genes, while pharmacogenomics is frequently used in an exploratory context such as genome-wide scans. Roses [22] made an important distinction between two types of pharmacogenetics. Safety pharmacogenetics is aimed at avoiding adverse drug reactions (ADRs). Efficacy pharmacogenetics is meant to predict response to medications.

3. The concept of biomarker in the literature

The term biomarker has many definitions, including the one proposed by Wagner [23], "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological response(s) to a therapeutic intervention." Some, then, are pharmacogenomic biomarkers and others are not [17,24]. Biomarkers play an important role in the pharmaceutical industry and are assuming an ever greater role in drug discovery and development [25].

The concept of biomarkers is introduced here, because in the spring of 2005 the Food and Drug Administration (FDA) developed guidelines for pharmaceutical companies on the collection and inclusion of genetic information for drug applications [26]. According to the FDA [26], genetic variants of two metabolic enzymes, CYP2D6 and Thiopurine S-Methyltranseferase (TPMT), were considered to be well established and, therefore, valid biomarkers. When submitting an investigational new drug (IND) application to the FDA, pharmaceutical companies must send relevant data on "valid biomarkers", although other pharmacogenetic data can be submitted voluntarily [27].

Since the "genomic" boom, technological advances have permitted the development of a new wave of tests and disciplines that can be considered within the concept of biomarkers. These include transcriptomic, proteomic and metabolomic tests which are being developed. Unfortunately, an announcement that a new technology is available does not mean that it has a good clinical use. In psychiatry, for example, limited data exist to support the use of blood cell expression to ably represent brain cell expression [28]. Current psychopharmacological knowledge suggests that peripheral markers, such as blood expression, may not be good biomarkers in pharmacogenetic studies for measuring brain neuron response to psychiatric treatments. Transporters at the blood-brain barrier may have an important role in the response to psychiatric drugs. Using peripheral biomarkers of psychiatric drug response may make more sense if one believes that some of the ADRs are related to peripheral mechanisms outside the brain, such as the possible direct influence of antipsychotics on lipid and glucose metabolism [29].

4. The concepts of personalized medicine and personalized prescription in the literature

The author has a preference for two terms usually related to pharmacogenomics and frequently used by lay journals: "personalized medicine" and "personalized prescription". "Personalized medicine" is described by Lesko [30] as "a comprehensive, prospective approach to preventing, diagnosing, treating, and monitoring disease in ways that achieve optimal individual health-care decisions." The idea of personalized medicine is that each individual may be different and needs to be treated differently by his/her physician. Ruaño [31] reminded us that physicians have traditionally practiced personalized

medicine in their attempts to decide the best treatment for each of their patients. However, physicians were not using the term "personalized medicine" and the personalized approach traditionally used by physicians was probably based on subjective physician preferences and not on scientific knowledge. In the view of this author, personalized medicine is a very global concept that may include "personalized surgery", "personalized rehabilitation", "personalized nutrition", and other types of personalized medical interventions and, more importantly for pharmacologists, "personalized prescription."

"Personalized prescription" was defined by a *Science* editorial [32] as "tailoring drugs to a patient's genetic makeup". That editorial in 1997 on the research horizons for 1998 predicted that personalized prescription would "soon" reach clinical practice [32]. Other more precise estimates for the generalized use of personalized prescription have been advanced: 2015 by *Time* magazine [33] and 2020 by *JAMA* [34]. If the generalized medical use of personalized prescription is going to occur in 7-12 years, one should notice preliminary steps toward its occurrence in the first generation of pharmacogenetic tests available in psychiatry (see Section 10). Even business journals [35] describe psychiatry (along with oncology) as being at the forefront in the use of pharmacogenomics in medicine. In the real world, the concept of personalized prescription has been wider than pharmacogenetics or pharmacogenomics. As a matter of fact, the first versions of two personalized prescription tests, for Trastuzumab (Herceptin) [36] and TPMT [37], usually did not include genotyping.

5. A personal view of personalized prescription as a concept extending beyond pharmacogenetics

In the opinion of the author [38], personalized medicine should include not only the use of biomarkers that may or may not be pharmacogenetic tests, but the consideration of all scientific information valid for prescribing medication. Pharmacology is a mechanistic science and knowing the pharmacological principles behind the response of a drug allows predictions to be made. For many drugs, genetic factors may be irrelevant in drug response or much less important than other non-genetic factors. Our pharmacological knowledge of each drug should determine what aspects are important in personalizing the prescription of that drug. In this comprehensive view of personalized prescription,

clinicians need to consider genetic, environmental and personal variables when prescribing any

medication [38]. If there are important genetic variables in the response to a specific drug they can be

explored by pharmacogenetic tests. Environmental variables such as co-medication, herb supplements,

foods, beverages, and smoking may be much more important than genetic factors for some drugs.

Personal factors such as age, gender, or medical illnesses (renal or hepatic insufficiency) may be crucial

personal variables in the response to some other drugs. Any classificatory attempt has to face the

complexity of and the lack of boundary between medical concepts [39], as there are no perfect definitions

of these genetic, environmental or personal factors affecting drug response. Genetic factors in drug

response can be defined as those requiring a pharmacogenetic test for identification. Environmental

factors come from outside the individual and are usually temporary. Personal factors are relatively stable

characteristics in a specific individual and usually recorded in the patient's medical history.

6. Personalized prescription should incorporate pharmacokinetic and pharmacodynamic knowledge

In the view of the author, to better apply the principles of personalized prescription one needs to

understand the influence of genetic, environmental and personal factors on the pharmacokinetics and

pharmacodynamics of each drug. Next is a short summary focused on antipsychotics, antidepressants,

mood stabilizers and benzodiazepines.

6.1. Pharmacokinetics of psychiatric drugs: a brief summary

Our knowledge of the pharmacokinetics of psychiatric drugs is relatively well developed in the

area of the Phase I metabolic enzymes (oxidation enzymes). Most psychiatric drugs are metabolized by

the cytochrome P450 (CYP) enzymes. Genetics are particularly important for two polymorphic CYPs, the

cytochrome P450 2D6 (CYP2D6) and the cytochrome P450 2C19 (CYP2C19). Unusual metabolizers,

including both poor metabolizers (PMs), who do not have active enzyme, and ultrarapid metabolizers

(UMs), who have too much active enzyme, have been described for both CYP2D6 and CYP2C19 [40,41].

Some rare subjects (<1/1000) are PMs for both CYP2D6 and CYP2C19 [42]. Section 9 describes the first

attempts to take CYP genotyping to the clinical environment. The cytochrome P450 1A2 (CYP1A2) and the cytochrome P450 3A (CYP3A) are also important for psychiatric drugs. They are heavily influenced by the environment and PMs and UMs for these CYPs do not exist or are very rare [40,43].

The CYP2D6 is probably a peculiar gene, since environmental influences on its activity are very limited. Normal CYP2D6 metabolizers, called extensive metabolizers (EMs), may look like PMs if they are taking a powerful inhibitor (e.g., fluoxetine, paroxetine, or bupropion) because the CYP2D6 is completely inhibited. CYP2C19, CYP1A2 and CYP3A can be inhibited and induced. CYP2D6 metabolism is important for some antipsychotics and some antidepressants [41]. CYP2C19 metabolism is important for some antidepressants and some benzodiazepines [41]. CYP3A metabolism is important for some antipsychotics, some antidepressants, some benzodiazepines and some mood stabilizers [43].

Of the Phase II metabolic enzymes (conjugation enzymes), the Uridine 5'- diphosphate glucuronosyltransferases (UGTs) are the most important enzymes for psychiatric drugs, including some antipsychotics, some antidepressants, some mood stabilizers and some benzodiazepines [44]. UGTs are less well understood and are neglected when compared with CYPs. Factors that contributed to this neglect include: 1) the overlapping activity of UGTs and the lack of selective probes, 2) the complexity of the glucuronidation cycle, and 3) the difficulty of developing analytic methods to measure glucuronides.

Transporters may be important, too. The P-glycoprotein, P-gp, is one such transporter. P-gp is an ATP-dependent efflux pump that is involved in the blood-brain barrier and may be important for absorption since it is located in the small intestine. P-gp has substrates, inducers and inhibitors that overlap with CYP3A. Several, but not all, antidepressants [45], antipsychotics [46], and possibly anticonvulsants/mood stabilizers [47] are substrates of this transporter to different degrees, suggesting that there may be differences between blood and brain concentrations, at least with some of these compounds. Moreover, there may be differences between a compound and its metabolites and, in the case of risperidone and its metabolite [48], this may contribute to differences in their ADRs and dosing [49, 50]. Renal excretion is important for some psychiatric drugs, particularly lithium, and may have some

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influence on risperidone and paliperidone clearance. A new generation of transporters may be important in renal excretion, but there is limited knowledge of their relevance for psychiatric drugs [51, 52].

Ideally, for each drug the contribution of genetic, environmental and personal variables should be taken into account when trying to predict dosing, but the literature only offers the initial attempts of pharmacokinetic models to estimate the relevance of these variables for psychiatric medications [53-57].

6.2. Pharmacodynamics of psychiatric drugs: a brief summary

The honest truth is that we do not have a clear understanding of how psychiatric drugs work. When using the same drug for different indications, pharmacokinetic variables may be common across psychiatric disorders but we are not sure that is true for pharmacodynamic targets, too. SSRIs are always metabolized in the same way independently of patient diagnosis, but SSRI pharmacodynamics may or may not be the same in depression as in anxiety disorders.

It is currently believed that the efficacy of antipsychotics is mainly explained by the blockade of dopamine D2 receptors. Some ADRs such as hyperprolactinemia and reversible extrapyramidal side effects are also mainly explained by D2 blockade [49]. Other frequent ADRs may be explained by the blockade of other receptors. Orthostatic hypotension may be explained by the blockade of α adrenergic receptors. Sedation is probably explained by the blockade of histamine and/or muscarinic receptors. Weight gain is probably explained by the blockade of histamine and/or serotonin 2_C receptors [49]. Constipation and dry mouth are probably explained by antimuscarinic properties. Other ADRs appear to have peripheral mechanisms, including disturbances in lipid and glucose metabolism and QTc increases in the heart [49]. Different antidepressants appear to work in different ways. Some are both serotonin and noradrenaline reuptake inhibitors; others are selective serotonin or noradrenaline reuptake inhibitors; others appear to influence multiple serotonin receptors or are monoamine oxidase inhibitors (MAOI) [58]. The brain receptors behind some antidepressant ADRs are similar to those of antipsychotics (adrenergic, muscarinic and histaminic receptors), but when combined with other serotonin drugs many antidepressants risk seriously disturbing the serotonin system by causing what is called serotonin

syndrome. Benzodiazepines are thought to act mainly by binding to GABA$_A$ receptors and increasing their affinity to GABA (allosteric modulators) [59]. The mood stabilizer mechanism of action is poorly understood; they may act through the cell-signaling pathways, the second messenger system [60].

One has to acknowledge that when compared with pharmacokinetic studies, pharmacodynamic studies in psychiatry present an additional level of complexity. The in vivo activity of pharmacokinetic factors can be explored by measuring blood levels. The only question left is how well blood levels reflect brain concentrations at important sites. The in vivo activity of pharmacodynamic factors can only be explored indirectly by brain imaging studies. These studies are limited by the expense and complexity of the technology and are characterized by small sample sizes; therefore, the information on genetic, environmental and personal variables in pharmacodynamics is almost non-existent. The clinical literature suggests that drug interactions, aging and some illnesses (e.g., Parkinson's disease for antipsychotics) are important environmental influences on pharmacodynamic targets [49].

The literature on the influence of genetics on pharmacodynamic variables for psychiatric drugs has presented major problems with replication. Section 10 describes the first attempt to create a pharmacogenetic efficacy test. The possibility of an association between weight gain and serotonin receptor variations may be one of the more promising leads, although it is far from clinical practice [61]. Section 10 also mentions the first attempt to develop pharmacogenetic testing for antidepressant pharmacodynamics. The complexity of mood stabilizer response makes pharmacogenetic efficacy testing an unlikely development in the near future [60]. There has been little interest in clinical studies on the pharmacogenetics of benzodiazepine response.

The literature [41] is beginning to suggest that the genetics of pharmacodynamic targets may be much more complicated than the genetics of pharmacokinetic factors. Recently, Nebert *et al* [18] have stressed the relevance of gene characteristics by proposing that pharmacokinetic genes tend to be high-penetrance and predominantly monogenic, while pharmacodynamic genes tend to be more polygenic. Similarly, Maier and Zobel [62] stressed the importance of gene effect sizes by proposing that

pharmacodynamic targets display a genetic influence of unknown magnitude emerging from the activity of multiple genes, each with only a small effect; on the other hand, pharmacokinetics reveals a documented strong genetic determination, which is mainly influenced by variants in a few genes.

7. Personalized prescription should pay attention to therapeutic window and prescriber's role

Drugs are approved in well-controlled studies that recommend an average dose and a range. These controlled studies increase the signal-to-noise ratio by reducing the noise; they exclude many patients and control treatment conditions. After drug approval physicians may utilize drugs differently than their use in clinical trials; therefore clinical practice brings more noise, including all kinds of patients, off-label use, co-medications, and varieties of doses and dosing schedules.

The last 15 years of drug development in psychiatry have been characterized by the transition from old, somewhat "toxic" drugs such as lithium, first-generation antipsychotics and tricyclic antidepressants (TCAs), to drugs that are much safer and have much wider therapeutic windows. In the opinion of the author, these pharmacoepidemiological facts are determinative in reference to the possibilities for success of personalized medicine in the clinical environment. The use of wider therapeutic window drugs makes the development of personalized medicine more difficult.

When physicians use toxic drugs with narrow therapeutic windows, they are severely restricted by the pharmacological makeup of the drugs, particularly their pharmacokinetics. High doses are toxic. Thus, drug pharmacology and pharmacokinetics are powerful signals for the older psychiatric drugs, limiting their noise. Using pharmacokinetic variables to personalize dosing of narrow therapeutic window psychiatric drugs has a high potential of being successful, due to the lower level of noise.

When doctors use newer drugs with wide therapeutic windows, they are freer to use wide dose ranges since they see little or no toxicity. In these situations doctor preferences or biases may be much more important than pharmacology in determining dose or drug selection [63]. When drug dosing is heavily influenced by physician choice it is much harder to predict the effects; thus the system has a lot of noise and the pharmacological signals may be lost in the noise [63]. Therefore, personalized dosing of

wide therapeutic window drugs may be quite difficult to develop or be completely irrelevant, since dosing in the real world of clinical practice may have little relevance in predicting drug response. The most complex cases are the wide therapeutic window drugs that also inhibit their own metabolism, such as paroxetine, fluoxetine or fluvoxamine [64]. They are poor candidates for personalized dosing [38, 65].

8. Safety personalized prescription should pay attention to the mechanism behind ADRs

ADR types are important and have not received enough attention in the pharmacogenetic literature. There are two main types of ADRs [66]. Type A (or pharmacological) refers to the augmentation of the pharmacologic action and is dose-dependent. Pharmacokinetic genes may be important for narrow therapeutic window drugs in that PMs will have ADRs. Pharmacodynamic genes may be important, too, for predicting Type A ADRs. Type B (or idiosyncratic) ADRs are not predicted by pharmacologic action. Two main mechanisms are suggested: peculiar idiosyncratic metabolic pathways leading to reactive metabolites and/or immunological response [67]. Pharmacokinetic genetic variations may be important for some of these type B ADRs, but this is unproven.

Some idiosyncratic ADRs are associated with the HLA system. HLA-B*1502 is strongly associated with the carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Han Chinese [68]. Genotyping for the HLA-B*1502 allele in persons with South Asian ancestry is FDA-recommended [69].

9. Personalized prescription can be implemented as personalized drug selection and/or as personalized dosing

The author believes that personalized prescription in the clinical environment can be expressed in two main ways: as personalized selection of the drug and as personalized dosing.

9.1. Personalized drug selection

Personalized selection of the drug has three levels: the first requires excluding some specific drugs in some unusual patients, the second requires matching some groups of drugs to some group of patients for purposes of greater efficacy or safety, and the third requires finding the best drug for each patient.

The first level of personalized drug selection is not controversial (Table 1) and refers to what has traditionally been referred to in medical practice as drug contraindication. The majority of the drug package inserts developed in the last 10 years provided information regarding safety contraindications that frequently include environmental and personal variables. An example of using an environmental variable to exclude a drug would be a drug-induced increasing QTc, contraindicating ziprasidone [70], and indicating the use of another antipsychotic with less risk of increasing QTc. An example of personal contraindication is to exclude psychiatric drugs with teratogenic potential in pregnant women. Only recently has the FDA focused on utilizing genetic tests to exclude drugs; using HLA-B*1502 genotyping to exclude carbamazepine, as described in the prior section, is a clear example. The author believes it is likely that other similar pharmacogenetic testing (or other biomarkers) may be developed in the near future, preventing some rare idiosyncratic ADRs. The main limitation in preventing rare idiosyncratic ADRs is the development of large pharmacological databases by interested research groups, some international, which may allow the identification of a sufficient number of these rare subjects. These databases are being developed for particular diagnoses [71]. An alternative to research groups focused on a peculiar idiosyncratic ADR is to conduct even larger studies by developing large DNA banks from multiple recruiting sites, collecting clinical information on ADRs in a systematic and unified way [72,73].

The second level of personalized selection includes exclusion of some drugs in some patients due to frequent ADRs or lack of efficacy. An example of a personal variable used to personalize antipsychotic selection would be that of using older age in females to exclude antipsychotics with a high risk of producing tardive dyskinesia, since older women have a much higher risk (e.g., one of our studies showed that the risk is 3 times as high in older women; their odds ratio was 3.0) [74]. An example of an environmental variable used to personalize antipsychotic selection is the use of weight gain to dictate prescription of an antipsychotic with a low risk of weight gain for the patient taking other drugs that increase appetite (e.g., lithium or valproic acid). As pharmacology, both pharmacodynamics and pharmacokinetics, varies across drugs, this second level of personalized drug selection has a reasonable

possibility of being successful. The main problem impeding its success is that the development of reliable tests for personalized drug selection is expensive. In the field of antipsychotics an interesting development has occurred in the area of cost-effectiveness. The second generation of antipsychotics is much more expensive than the old antipsychotics [75,76]. But now it is becoming clear that second-generation antipsychotics may not be better, and certainly they are less cost-effective [77, 78]. First-generation antipsychotics generate more risk of tardive dyskinesia (particularly those with high potency) and some may promote metabolic syndrome (particularly those with high potency). A reasonable alternative from the public health point of view may be to use the cheaper antipsychotics with pharmacogenetic tests that decrease their ADRs. The difference in cost (hundreds versus thousands of dollars per year) may accommodate a few hundred dollars for pharmacogenetic testing. This testing may be CYP-based or new tests may be developed that could be used in the prevention of tardive dyskinesia [79] or metabolic syndrome [80,81]. However, US society may not want to go back to older, cheaper drugs [76].

The third level of personalized selection, which includes choosing the best drug for the average patient, is much more controversial and difficult (Table 1). The controversy is that important economic benefits may be derived for most frequently selected drug. The difficulty is that selection of a previously unused drug is a very complicated process since it requires considering risk versus benefits, safety versus efficacy. The author has no non-controversial examples of personal or environmental variables that can help at this level of personalizing drug selection. In summary, the personalized selection of a drug for the majority of patients may be a very difficult issue to implement in the clinical environment, due to the economic implications and also to the complexity of developing methods balancing both safety and efficacy. As indicated in Section 6, although safety mechanisms may be common to various indications, efficacy mechanisms may vary for the same drug for different indications.

9.2. Personalized dosing

Once a specific drug is selected, using pharmacology for the implementation of personalized dosing is easier; pharmacodynamic and pharmacokinetic knowledge of dosing is clear.

The experience of the author suggests that practicing clinicians can easily understand personalized dosing using pharmacokinetic principles as long as the drug follows linear kinetics. Many psychiatric drugs follow linear kinetics, and that probably includes antipsychotics [43]. As previously indicated, fluoxetine, paroxetine and fluvoxamine are auto-inhibitors; therefore they do not follow linear kinetics. Some of the mood stabilizers that are auto-inducers, such as carbamazepine or lamotrigine, may not follow linear kinetics and their kinetics change over time. The beauty of linear kinetics is that concentration (C) and dose (D) follow a linear relationship with a stable C/D ratio. Thus, if one increases D by 2, C as an average will increase by 2 and if one decreases D by 2, C as an average will decrease by 2. Wong et al. [82] reported that phenytoin increases the oral clearance of quetiapine by 5; this would require, on average, a fivefold increase of D to maintain the same C. If one uses an average quetiapine D of 700 mg/day, to compensate for phenytoin the average D would need to be at least 3500 mg/day.

Pharmacodynamic factors may also be important in personalizing dosing. The dopamine D2 receptors (DRD2) are definitely important in explaining antipsychotic-induced EPS. Let us imagine that a genetic abnormality interferes with the DRD2 gene. This would certainly increase the risk of EPS. Unfortunately, no such genetic variation has been identified [61].

Table 1 describes two levels of complexity in personalizing dosing. These two levels are based on a drug's therapeutic window. The narrower the therapeutic window (or index) of the drug, the more important personalized dosing becomes.

A narrow therapeutic window means that once we have reached an efficacious D, it is relatively easy to move to the unsafe D. In narrow therapeutic window drugs, pharmacodynamic variables may be important in personalizing dosing regarding safety but pharmacokinetic variables are definitely important in that regard. In narrow therapeutic window drugs, the influence of genetic, environmental and personal factors on pharmacokinetic factors may make the patient behave as a PM. This means that with unexpectedly low D he/she may have a high C. The way to correct an increased C/D ratio is by lowering D. High C determines only the increased risk of Type A ADRs; it does not determine the specific ADR.

Although it has not been studied, the effects of genetic (or environmental or personal) variability on pharmacodynamics may determine the specific ADR. For example, the presence of a high C/D ratio in a patient taking R can be explained by CYP2D6 PM status (a genetic reason); use of paroxetine, a powerful CYP2D6 inhibitor (an environmental reason); or renal insufficiency (a personal reason), each of which decreases R elimination. All of them promote high R C. We cannot predict which ADRs may manifest. Any of the frequent R ADRs are possible: extrapyramidal symptoms (EPS), sedation, orthostatic hypotension, or gastrointestinal symptoms. The presence of one or another may be explained by pharmacodynamic factors including genetics.

If the drug has a very wide therapeutic window, personalized dosing may not be too relevant; dosing may have relatively little influence on safety and efficacy. In the real world, the prescriber's decision concerning dosage may be much more important than pharmacology, thus complicating the process of implementing personalized dosing using biomarkers or pharmacogenetic tests. As previously indicated, efficacy biomarkers may be difficult to develop. Safety biomarkers, including pharmacogenetic testing for personalized dosing, may have some potential for wide therapeutic window drugs if dosing influences the presence of ADRs in the clinical environment.

Due to limited space, this perspective article cannot explain how personalized dosing may be of practical use in the real world. Prior articles focused on how genetic, environmental and personal variables influence the pharmacokinetics and pharmacodynamics of risperidone [49,50] and how pharmacogenetic testing and blood levels can be used to predict risperidone dosing [54].

10. Pharmacogenetic testing in psychiatry at present

The current status of pharmacogenetic testing in psychiatry, which was the focus of two prior articles [83, 84], does not look particularly promising. Of the five tests described in peer-reviewed publications, the one which focused on using antipsychotics safely in regard to metabolic syndrome is not on the market, but the company hopes to seek FDA approval in the future (PhyzioType test) [80]. Another of the five tests focused on idiosyncratic ADRs and was on the market for less than a year, due to

insufficient sensitivity and specificity (PGxPredict:CLOZAPINE) [85]. The third was an efficacy test

(LGC clozapine test) using only British subjects [86], meaning that replication in other subjects may be an

issue [61]. Finally, lack of clinician use appears to be an issue for the two marketed CYP tests [87], one

of which only measures CYP2D6 PMs and CY2C19 PMs well (Luminex Tag-It[TM] Mutation Detection

Kit). The other (the AmpliChip CYP 450 Test) includes more alleles, particularly those associated with

the CYP2D6 UM phenotype, and is more expensive [86]. However, the clinical use of these two CYP

tests is limited in that the older drugs with narrow therapeutic windows (TCAs and typical antipsychotics)

were not included, and they are of limited use for new drugs (perhaps for risperidone). The two CYP tests

are also limited by the sparse clinical evidence available [41,88] and by lack of psychiatrist education

[89]. The use of serotonin transporter gene promoter variation to predict antidepressant response may be

doomed by the complexity of the clinical issues and by lack of knowledge of the phenotype-genotype

relationship [84]. An attempt to resuscitate an unmarketed psychiatric drug iloperidone, using

pharmacogenomic testing, has not been successful [84].

11. The future of pharmacogenetic testing in psychiatry

Let's start with the positive aspects as we look toward the future, namely, that genetic technology

continues to surprise with meaningful new advances that may have relevance for testing in the clinical

environment. A new nanotechnology can provide genotyping results in a few hours, providing busy

clinicians with rapid answers [90]. The FDA approved a warfarin test using this technology in September

2007 [91]. It is currently unclear how epigenetic changes can be tested in the clinical environment, but

Marsh [92] suggested that pyrosequencing may be a flexible technology that can be used for testing SNPs,

CNVs, and also methylation status.

HLA-B*1502 genotyping in Asians, a test developed in neurological patients, should be used in

psychiatric patients taking carbamazepine. The role of this test is very limited; it is a pharmacogenetic test

for one drug and for one racial group, and only eliminates the risk of relatively rare idiosyncratic ADRs.

Clinicians have complained to this author that such an advance is miniscule. Unfortunately this is the only

pharmacogenetic test in the immediate future of psychiatry that has definitive support for its clinical indication. It is possible that some other test for the detection of some other unusual idiosyncratic reaction to psychiatric drugs in a racial group may be developed in the next five years.

Currently, CYP2D6 and CYP2C19 genotyping appear to have little future (see the next section for possible reasons). Pharmaceutical companies are eliminating drugs metabolized by CYP2D6 from their pipeline. As indicated in Section 9, first-generation antipsychotics may be as efficacious as the new ones. As they are much cheaper, marketing the use of first-generation antipsychotics plus personalized tests may be the way to go. Unfortunately, this idea is contrary to the current marketing strategies of the pharmaceutical companies which are promoting second-generation antipsychotics.

This article defines a new way of looking at personalized prescription, describing it as the use of genetic, environmental or personal information for selecting drugs and/or prescribing dosages. It also proposes that, in the case of many drugs, personalized prescription is likely not to include genetic testing. With this broad definition, personalized prescription can be utilized. It requires only that sophisticated clinicians understand that genetic, environmental or personal variables influence pharmacokinetic and pharmacodynamic response; the therapeutic window of the drug may be important, too. Blood levels, currently called therapeutic drug monitoring (TDM), have been used by psychiatrists to personalize dosing for lithium, TCAs and some antipsychotics [93]. Unfortunately, all of these are old drugs rarely used by young prescribers in psychiatry. The marketing of the new drugs has convinced psychiatrists that they do not need to use these old drugs, thereby using TDM in psychiatry appears irrelevant. It also makes teaching this broad view of personalized prescription difficult.

12. The limited future of pharmacogenetic testing in psychiatry

Every year for the past five years, this author has become more pessimistic regarding personalized prescription. He further ruminates that there is not much "future" for it in the next five years in psychiatry; only small incremental steps appear possible. The obstacles to progress for personalized prescription in psychiatry appear insurmountable. These obstacles have been reviewed in prior articles

[82,83,86,88] and include: 1) the lack of interest among funding agencies for pharmacogenetic studies in the real world; 2) the lack of enthusiasm among pharmaceutical companies for pharmacogenetic testing; 3) the difficulty of publishing pharmacogenetic studies focused on real world questions; 4) financial issues (a new diagnostic test may have limited benefit, whereas a drug might become a blockbuster and make millions of dollars); 5) the lack of training for physicians in the use of the new pharmacogenetic tests; and 6) the lack of prior approval of pharmacogenetic tests, which means facing a different type of regulatory oversight than used for drug approval. This perspective article emphasizes 7) the complexity of the methodological/scientific issues in personalized prescription; added to the prior six obstacles. This complexity has led to the virtual absence of controlled studies in the real world designed to explore pharmacogenetic testing in psychiatric clinical practice.

Pharmacogenetics appears to be progressing faster in psychiatry than in other areas of medicine, with the possible exception of oncology. However, when psychiatry is compared with oncology, oncology certainly appears to have a brighter future in terms of using biomarkers to personalize prescription because oncology has easy access to tissue, as well as a better understanding of the complex pathophysiological mechanism. Not all of these biomarker tests for personalized prescription will be pharmacogenetic tests. As a matter of fact, some of the tests used in the clinical practice of oncology for personalizing prescriptions are not pharmacogenetic tests. Cancer's lack of stigma (compared with the stigma associated with mental illness) and the lethality of the oncological diseases, combined with the high toxicity and the high cost of oncological drugs, may make personalized prescription in oncology easier to sell and more cost-effective than in psychiatry. As a matter of fact, CYP2D6 genotyping may be getting a second life in oncology since tamoxifen may not have protective effects against breast cancer in CYP2D6 PMs [94].

This perspective article further elaborates on a previously neglected obstacle, the complexity of the scientific task of resolving the conceptual issues behind personalized prescription. Currently, the author thinks that, in psychiatry, pharmacogenetic tests or other types of complex biomarkers have some

potential in two areas: 1) excluding the use of some drugs for some unusual patients (has major potential since neurology provided the first pharmacogenetic test for carbamazepine), and 2) personalizing drug dosing by using pharmacokinetic genes in narrow therapeutic window drugs (has some potential but these drugs may be irrelevant for clinical practice unless the old antipsychotics are returned to use). There is dubious potential for: 1) selecting some drugs within a class due to ADR or efficacy profile, and 2) selecting dosing in a wide therapeutic window drug. The author thinks that there is no short-term potential in finding the best drug for each patient. This "very sophisticated" level of personalized prescription is beyond our current knowledge and study methodologies.

13. Conclusions

In conclusion, this perspective article has an "ambivalent" message. The pessimistic aspect is that the future of pharmacogenetic testing or other biomarkers in personalizing prescription in psychiatry does not look promising, other than the limited examples noted, which are not widely used. However, if one looks closely at both components of personalized prescription, personalized drug selection and personalized dosing, it is obvious that personalized dosing has immediate application if one understands it as the use of our current scientific knowledge of genetic, environmental and personal variables to determine dosing. Nevertheless, there is need to complicate the picture by bringing to bear other pharmacological concepts such efficacy versus safety, pharmacokinetics versus pharmacodynamics, narrow versus wide therapeutic window drugs, and dose-related versus idiosyncratic ADRs.

The optimistic aspect is that pharmacological information on drug-drug interactions and personal variables plus pharmacogenetic tests and TDM can currently be used to personalize dosing, particularly for narrow therapeutic window drugs. A major limiting factor is the lack of well-trained psychiatrists who use pharmacological principles to personalize prescription in psychiatry. These sophisticated psychiatrists will be needed in the future to incorporate new pharmacogenomic testing or other biomarker tests to personalize prescriptions in psychiatry.

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Table 1. Levels of complexity of pharmacogenetic testing as an aid to personalized prescription in psychiatry

1. PERSONALIZED DRUG SELECTION
1.1. Exclusion of some drugs for some unusual subjects
Easily done and non-controversial
Pharmacogenetic testing may identify individuals with high risk of idiosyncratic ADRs
Pharmacokinetic genetic testing may identify PMs taking pro-drugs (lack of efficacy)
Pharmacokinetic genetic testing may identify UMs taking pro-drugs (safety)
Pharmacodynamic genetic testing may identify variations associated with no response (lack of efficacy)

1.2. Exclusion of some drugs within one class in some patients due to frequent ADRs or lack of efficacy
To be developed: who will pay for the complex studies (better pharmacological understanding is needed)
Will cost differences between old drugs and new drugs pay for testing if used in clinical practice?
Unclear that pharmacokinetic genes have major effects (small effects are likely)
It is possible that pharmacodynamic genes may play a role but they need to be identified

1.3. Selection of best drug for each patient
Controversial: important economic benefits may be derived for most frequently selected drug
Public health point of view: Drug cost may need to be considered
Patient's point of view: Drug with good risk-benefit balance (safety-efficacy)
Unusual pharmacokinetic gene variations can be handled by dosing changes (see below)
Pharmacodynamic gene variations require balancing risk-benefit and safety-efficacy
It may not be easy to match individual genetic profiles and many different drugs
Models combining genetic, environmental and personal variables may be too complicated
It is not understood how prescribers' and patients' attitudes and beliefs influence drug selection
Study replications may be a major problem (too much noise)

2. PERSONALIZED DRUG DOSING
2.1. Drugs with narrow therapeutic window
Easily done: recent package inserts include some "personalizing" information regarding safety
Using pharmacogenetic tests has potential but it is in its infancy:
i) PMs (genetic or taking inhibitors) need low doses to avoid ADRs (safety)
ii) UMs (genetic or taking inducers) need higher doses (efficacy)
Pharmacokinetic models need to consider genetic, environmental and personal variables
Pharmacodynamic genetic tests may be helpful for safety (decrease dosing): not clinically available
It is not known if pharmacodynamic genetic tests may be helpful for efficacy

2.2. Wide therapeutic window drugs
Not easily achieved: drug pharmacology may have small effects in determining dosing
Prescribers' attitudes and beliefs may introduce much noise in the system
PMs (genetic or taking inhibitors): may have limited relevance for avoiding ADRs (drugs are safe)
UMs (genetic or taking inducers): may only have relevance in extreme case (lack of efficacy)
Unknown whether pharmacodynamic genetics will be robust enough in tests for safety or efficacy

ADRs: adverse drug reactions. PMs: poor metabolizers. UMs: ultrarapid metabolizers.