COMMENTARY

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Pharmacogenetics and Pharmacovigilance

Robert H. Howland

University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, USA

Many different types of drugs are available to treat a wide variety of disorders. Why some patients respond to a particular drug and others do not respond, or why some patients tolerate a drug well and others are intolerant of the same drug, are obviously important clinical issues in medicine. Genetic differences among patients may contribute to differences in medication response, as well as the development of adverse effects.[1,2] 'Pharmacogenomics' and 'pharmacogenetics' are terms that refer to the use of molecular genetic approaches to understand differences in drug response and tolerability. Although the two terms are sometimes used interchangeably, pharmacogenetics is, more specifically, the study of specific single nucleotide polymorphisms (SNPs) at specific genes with known functions that could plausibly be linked to drug response, whereas pharmacogenomics refers to whole genome scanning to find SNPs that might be associated with a drug response, but without necessarily knowing the function of the identified SNPs.

One approach to understanding pharmacogenetic differences in drug response and tolerability is through the study of pharmacokinetics.[2] In this issue of *Drug Safety*, van Puijenbroek and colleagues[3] describe the results of a study whose objective was to investigate the feasibility of a method for informing physicians or pharmacists who report adverse drug reactions (ADRs) about the possible involvement of a genetic polymorphism in the ADR and to recommend subsequent genotyping of patients based on this possibility. The method involved the review of spontaneous ADR reports received by the Netherlands Pharmacovigilance Centre (NPC). Trained assessors at the NPC (a physician or pharmacist) evaluated each ADR report. For this study, reports were included if there was a strong suspicion by the NPC assessor of involvement of a possible genetic polymorphism of the cytochrome P450 (CYP) 2D6, 2C19 or 2C9 hepatic metabolic enzymes relevant to the drug in question. After identification of an eligible case, a feedback letter was sent by the NPC to the ADR reporter describing the study and the recommendation for genotyping. Whether genotyping was conducted was at the discretion of the patient's treating physician.

Based on their findings, van Puijenbroek and colleagues[3] concluded that the strength of a pharmacovigilance centre is that it can combine information from different sources in the assessment of the causal relationship between intake of drugs and ADRs, and, based on this information, that it can initiate genotyping of patients for polymorphisms in drug metabolizing enzymes (DMEs). Although the concept of incorporating pharmacogenetic information into a pharmacovigilance system makes sense in theory and has potentially important personal and public health implications, the clinical utility of a system is only as good as the individual components. The system described in this paper illustrates many of the real and potential problems in applying pharmacogenetic technology to pharmacovigilance and patient care.

The interpretation of ADR reports is important for pharmacovigilance and pharmacogenetic studies. Establishing causality between drug use and a 'reaction' is a difficult and complex process.[4,5] For a patient taking a drug or

drugs, are the reported signs and symptoms of the 'reaction' due to the drug(s), the treated illness or to other factors? Although healthcare providers are strongly encouraged to report suspected ADRs, various factors may positively or negatively bias the recognition and reporting of ADRs.[6] Just because a patient taking a drug reports an adverse effect to their physician or pharmacist does not mean that the drug and the effect are definitely or plausibly linked. Patients taking placebo in placebo-controlled drug treatment studies can report adverse effects that are similar to those known to be related to the drug under study. From a psychological perspective, expectancy and conditioning theories have been used to explain the placebo effect.[7,8] The expectancy theory proposes that the expectations or beliefs that patients have about treatment will influence how they respond to treatment. Such expectations may be conscious or unconscious. Patients who have positive expectations that treatment will help demonstrate a significantly higher level of response to an active medication compared with those patients with less positive expectations who are taking the same medication.[9] Patients with positive expectations may therefore show improvement even if they are only taking a placebo.

By contrast, negative expectations may have a deleterious effect. As a result, some patients may develop noxious adverse effects with a placebo. This effect has been termed the 'nocebo' effect.[10] Similarly, positive or negative expectations harboured by treatment providers may subtly (or not so subtly) affect what patients believe will happen with treatment, and this may contribute to placebo and nocebo effects. Conditioning theory proposes that past experiences may lead to learning (conditioning) that contributes to symptom changes or adverse effects. This process is more unconscious. There is some debate about the extent to which expectancy and conditioning effects can be distinguished from each other to explain placebo effects, and even whether conditioned placebo effects without expectancies are prominent in people.[11] Placebo effects have been demonstrated in animals, and it is likely that this effect is explained by Pavlovian conditioning.[12] It is possible that conditioning might be somewhat more relevant for explaining the development of nocebo effects in people, through negative past experiences and aversive learning.[10,13]

Many types of putative ADRs are likely to be complex and to have multifactorial etiologies. Examples include weight gain,[14,15] the metabolic syndrome,[16,17] tardive dyskinesia,[18] suicidality,[19] hepatic dysfunction[20] and cardiac abnormalities.[20] These conditions are clinically significant and often linked to drug therapies, but they cannot be easily or solely attributed to a drug exposure. Establishing a valid link between an ADR and an underlying genetic polymorphism depends, in part, on using accepted criteria for an unambiguous diagnosis of the ADR.[20]

From a clinical perspective, ADRs can be generally classified into one of two subtypes.[21] Type A ADRs are related to a drug's known pharmacological effect, they occur more frequently and constitute the majority of all ADRs of a drug, are typically dose-related, and are often predictable and potentially preventable. Type B ADRs are idiosyncratic and unpredictable, are not clearly related to the drug's pharmacological effect, are not necessarily dose related and are less readily preventable. Both types of ADRs are clinically important and each may be serious or severe, but type B reactions often carry a proportionately greater risk of significant morbidity or even mortality. From a genetic perspective, ADRs can be categorized according to their relationship with DMEs (pharmacokinetics), drug targets (pharmacodynamics) or immune response genes (e.g. human leukocyte antigen [HLA]).

From reviewing the 38 reported ADRs described in tables I and II of the study by van Puijenbroek and colleagues,[3] it is not completely clear why these particular reactions prompted the NPC assessors to recommend pharmacogenetic testing. By what criteria did the assessors in the study decide that an ADR was attributable to underlying pharmacogenetic factors rather than to other non-genetic factors? In general, how would an independent assessor decide that a reported adverse effect for a particular drug would be worthy of further pharmacogenetic testing? Of the 38 ADRs reported in the study, 15 were judged

to be 'serious' by the reporter (one case was life threatening, five cases led to hospitalizations and nine cases were associated with other medically important conditions), but the authors do not explain the putative pharmacogenetic link between the drug and the ADR that would justify their recommendation for genotyping in any of the 38 cases.

In their paper, van Puijenbroek and colleagues[3] assert that "assessors of a pharmacovigilance centre may suspect a possible pharmacogenetic involvement, but the decisions whether or not to have the patient genotyped should be made by the treating physician. Based on the information provided by the reporters, a reliable selection cannot be made by the pharmacovigilance centre itself. The role for the pharmacovigilance centre is to make the reporter aware of the fact that genetic factors may play a role in the occurrence of the ADR. It is up to the physician to decide if additional testing should take place. Since the role of the pharmacovigilance centre is only to provide information about the possible role of a pharmacogenetic factor, no strict criteria were in place to select possible candidates for genetic testing."

This stance undermines the project's potential value as a vehicle for pharmacovigilance, limiting it to an advisory and educational role. Although 'advice' and 'education' are important for physicians and pharmacists, particularly with the early clinical application of emerging technologies such as pharmacogenetics, the ambiguous method described by van Puijenbroek and colleagues[3] does not seem suitable for providing appropriate clinical and scientific information about pharmacogenetics testing. This system seems to depend on the apparent arbitrary judgment of the NPC assessors. Ideally, ADR incidence should be reduced if drug selection and dosing were based on genetic variability. Whether the process outlined would be truly beneficial for individual patients, or more generally for pharmacovigilance of larger populations, is therefore questionable.

The stated aim of the study by van Puijenbroek and colleagues[3] was to gain insight as to the feasibility of informing the reporting physician or pharmacist about possible involvement of a genetic polymorphism and subsequent genotyping of patients based on ADR reports received by the NPC. Remarks or suggestions regarding the procedure from health professionals or patients were to be noted. Obtaining this type of information from a feasibility study would be very important, but the authors report no data. Of 6778 ADR reports to the NPC, 38 cases were selected by NPC assessors and recommended for genotyping. Of these 38 cases, genotyping was conducted in only 15 patients (39.5%) and eight of these patients were found to carry genetic polymorphisms of one of the three CYP enzymes. Physicians reported 23 of the 38 ADR cases to the NPC; pharmacists reported the other 15 cases. Only eight of the 23 physician-initiated ADR reports (34.8%) led to genotyping, compared with seven of the 15 pharmacist-initiated reports (46.7%). For the 15 genotyped cases, what did the professionals and patients think about this system? Why did they participate? Why were pharmacist-initiated reports more likely to result in genotyping than physician-initiated reports? Were the results of the genotyping ultimately helpful in any way? For the 23 cases not tested, it would have been important to understand why they did not participate. What were the problems or limitations? The authors conclude that health professionals viewed genotyping as being 'important' to do and suggested that the "consequences for future pharmacotherapy in the individual patients may have contributed to this relatively high response" to the NPC recommendation for genotyping. However, the low participation rate (39.5%) and the lack of data about how the information was used do not support this conclusion. Based on this study, we do not know whether this reporting system had any real value to the professionals who participated and why the remaining professionals did not participate.

In their paper, van Puijenbroek and colleagues[3] maintain that "for pharmacovigilance centres, information on the presence of polymorphisms in genes encoding drug-metabolizing enzymes provides a valuable contribution in the analysis of the causal relationship between the suspected drug and the ADR", and that "the individual patient should be informed about

the existence of genetic polymorphisms that influence the occurrence of the ADR, so that future treatment with drugs metabolized by the enzyme involved can be administered at an appropriate dose". This claim overstates the current clinical utility of pharmacogenetic testing, without acknowledging and discussing the clearly known limitations of pharmacogenetic science and technology.

For this study, van Puijenbroek and colleagues[3] limited their genotyping to CYP2D6, CYP2C19 and CYP2C9, but they do not explain why other metabolic enzymes were not included in the analysis.[22] In their large systematic review of the potential role of pharmacogenomics in reducing ADRs, Phillips et al.[23] noted that the CYP1A2 enzyme has only one identified variant allele with poor metabolism, but there is a significant prevalence of poor metabolizers (PMs) of CYP1A2 substrates among the Caucasian population. CYP1A2 is estimated to be the major metabolic pathway for only 5% of all prescribed drugs, but is at least partly involved in metabolizing 75% of the ADR drugs associated with variant alleles. Hence, CYP1A2 might play a more important role in ADRs than previously appreciated. CYP2D6 is estimated to be the major metabolic pathway for 25% of all prescribed drugs and is widely suspected of causing ADRs because it has a multitude of known variant alleles, but CYP2D6 has a slightly lower prevalence of PMs (3–10% among the Caucasian population) than CYP1A2. Phillips et al.[23] found CYP2D6 to be involved in metabolizing 38% of the relevant ADR drugs, which was less than what is observed for CYP1A2. They suggested that these results may indicate an increasing awareness of CYP2D6 variants as a complicating factor in drug therapy, leading clinicians to select non-CYP2D6 drugs if severe adverse effects are believed to be likely. This potential bias based on perceived notions of drug metabolism and drug safety illustrates the problem of developing a pharmacovigilance feedback system for clinicians, which does not have appropriate and clearly established screening procedures for identifying ADRs, and which does not have the technological capacity to assay a wide variety of metabolic enzyme genotypes.

In the study by van Puijenbroek and colleagues,[3] the majority of the drugs implicated in causing the ADRs were selective serotonin reuptake inhibitor (SSRI) antidepressant drugs, followed by other antidepressant drugs and antipsychotic drugs. A recently published evidence report from the US Agency for Healthcare Research and Quality broadly reviewed existing studies to determine if testing for CYP polymorphisms in adults taking SSRIs for depression leads to improvement in outcomes or if testing results are useful in medical, personal or public health decision making.[24] One particular issue addressed in the report was how well CYP testing predicted ADRs and whether factors such as race/ethnicity, diet or other medications affect this association. The authors identified nine studies, three of which reported adverse effects in CYP PMs only as a secondary finding. Of the other six studies, three reported no differences in rates of adverse effects between CYP2D6 PMs and extensive metabolizers (EMs), while a fourth study reported no differences in adverse effects between the combined PM plus intermediate metabolizer group and the combined EM plus ultra-rapid metabolizer group. One study found a greater prevalence of gastrointestinal adverse effects in PMs compared to EMs. This study also found that the combination of CYP2D6 polymorphism and serotonin 5-HT_{2A} receptor polymorphism predicted gastrointestinal adverse effects. Two studies found a significantly higher prevalence of PMs in depressed patients with adverse effects than in the general population. The studies had several limitations, including non-randomized design, inadequate power and not accounting for other genetic factors that may influence SSRI tolerability (e.g. genetic variations in serotonin receptor proteins). The literature review revealed a paucity of high-quality clinical studies addressing their main objectives. In particular, there were no prospective studies of CYP genotyping and its relationship to clinical outcomes. The data failed to support a clear correlation between CYP polymorphisms and SSRI blood levels, SSRI efficacy, or tolerability. There were no data regarding whether testing lead to improved outcomes versus not testing in the treatment of

depression; whether testing influenced medical, personal or public health decision making; or whether any harms were associated with testing itself or with subsequent management options. Similarly, the clinical utility of genotyping DMEs for other drugs has not been established.[22]

In addition to DMEs, ADRs can also be associated with genetic variations in drug targets (pharmacodynamic effects) as well as immune response genes (e.g. HLA). In their study, van Puijenbroek and colleagues[3] excluded patients who died and patients who reported allergic reactions. Both types of ADRs, falling into the category of type B reactions, would be particularly important for a pharmacovigilance programme and for feedback to clinicians. The incidence of fatal ADRs is as high as 3%.[25,26] Pharmacogenetic feedback to physicians reporting a patient death related to an ADR would be potentially valuable information for the future care of other patients. Moreover, if a pharmacogenetic link was established with a drug in a particular patient, such information would also be potentially important for first-degree relatives of the deceased patient. Although the authors state that patients with an alleged allergy for the suspected drug were excluded because ''a genetic involvement in the pathogenesis is unlikely in the event of an allergic reaction'', approximately 20% of ADRs may have an immunological etiology.[27] One recent example is the identification of a genetic risk factor for carbamazepine and phenytoin reactions.[28] Serious and sometimes fatal dermatological reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported in patients of Asian ancestry with the inherited allelic variant *HLA-B*1502*. Genetically at-risk patients should be screened prior to receiving these drugs and the drugs should not be started in patients who test positive for the allele.

The current clinical utility of a pharmacovigilance programme that incorporates pharmacogenetic information is also extremely limited by the sheer complexity of the genome. The importance of epistasis (gene-gene and gene-environment interactions)[29] and epigenetics (non-DNA sequence-related heredity)[30] in genomics research is growing rapidly, but is largely unexplored in pharmacogenetic studies. Much of the variance in findings from pharmacogenetics studies conducted to date may be explained in the future by currently unknown epistatic or epigenetic effects. For these reasons and the reasons I have outlined in this commentary, the development of a system to use a technology (pharmacogenetics testing) whose clinical utility has not yet been established is premature. Moreover, a multitude of regulatory, ethical, social, legal and cost-effectiveness issues need to be addressed with the use of pharmacogenetics testing before such a system is employed.[31-33]

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Correspondence: Dr *Robert H. Howland*, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA.
E-mail: HowlandRH@upmc.edu