



Pharmacogenomic profiling in postmarketing surveillance: prospects and challenges

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Adverse drug reactions represent a major public health and economic global problem. Growing evidence suggests that pharmacogenomics may potentially play a role in reducing drug-induced adverse events. Research efforts are increasingly directed towards this goal. However, knowledge about whether or not pharmacogenomics may be useful as a novel approach in postmarketing surveillance programs is at present rather limited. A critical analysis of some of the methodological design and ethical issues generated by the potential incorporation of pharmacogenomic profiling into pharmacosurveillance programs is presented.

Introduction

Developments in pharmacogenomic technologies, such as single nucleotide polymorphism (SNP) analysis, automated gene sequencing and the proliferation of databases, promise to herald a new era in drug discovery, development and therapeutics. The applications of pharmacogenomics and how they will impact the pharmaceutical industry and the provision of healthcare have been reviewed by several authors in the last 3 years [1-8].

The promise that pharmacogenomic applications might overcome the serious public health problem of adverse drug reactions (ADRs) is one goal of current research efforts. However, despite the promise of anticipated benefits, the feasibility of pharmacogenomics as a tool of pharmacosurveillance in the postapproval period of therapeutics has not been well addressed.

This article focuses on the potential utility of pharmacogenomics for postmarketing surveillance, including examples, and some of the methodological and ethical implications that deserve more critical analysis.

Some relevant definitions

It has become increasingly customary to begin a review of this topic by defining the distinctions between the terms 'pharmacogenetics' and 'pharmacogenomics' and many slight and not so slight variations have been proposed [9-12]. However, it is also clear to researchers in the field that the two terms are used interchangeably and that there appears to be considerable overlap in what these two terms encompass, although most acknowledge that, in principle, pharmacogenomics encompasses a broader spectrum of

genomic technologies and applications focused on drug research and development and potential clinical utility. In this paper, the focus is on one aspect of pharmacogenomics: its anticipated usage in minimizing or eliminating ADRs.

For the purposes of this article, ADR is defined as 'any noxious, unintended and undesired effect of a drug which occurs at doses used in humans for prophylaxis, diagnosis or therapy,' according to World Health Organization (WHO) criteria [13]. Thus, adverse events due to overdose, drug abuse or drug administration errors are excluded.

The application of genomic technologies to associate genetic polymorphisms with particular phenotypes, such as specific ADRs, can be referred to broadly as pharmacogenomic profiling [1]. The discipline of pharmacoepidemiology is concerned with applying the tools of epidemiology to therapeutic drugs and their outcomes, including adverse events as well as therapeutic benefit. The scientific practice relating to understanding, detecting and preventing drug-related adverse events and other problems is known as pharmacovigilance or pharmacosurveillance [14].

The public health challenge of adverse drug reactions

It is well known that ADRs are a major challenge to the health of populations [15-21]. In the United States, several highly cited reports have highlighted that ADRs are among the leading causes of serious morbidity and mortality among hospitalized patients [16,17]. In the United Kingdom, studies have shown that the prevalence of ADRs is a leading cause of hospital admissions [20,22]. Studies conducted in Switzerland [23,24], France

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[25] and Australia [19] demonstrated similar findings. A recent prospective cohort study conducted at four primary care practices in Boston reported that in over 600 adult out-patients monitored, there was a one in four incidence of an ADR [21]. This suggests that ADRs are a serious problem in the out-patient population as well. It is evident, therefore, that ADRs are a common global problem across a variety of healthcare systems.

Several systems have been suggested to categorize ADRs depending on the nature of the ADRs and their mode of action or pathways [26,27]. The current method of classification has evolved to include six categories that can easily be remembered according to an alphabetical nomenclature with mnemonic features [26,27]:

- Type A reactions, labeled 'augmented' under the present classification scheme, are those that are dose-related and depend on the pharmacological properties of the drugs in question. Adverse events, such as dizziness and diplopia, are examples of type A reactions. Adjustment of dose usually resolves type A adverse events.
- Type B or 'bizarre' reactions are not usually dose-related but tend to be idiosyncratic, rare and frequently patient specific.
- Long-term adverse effects seen after prolonged use of a drug are termed type C or 'chronic.'
- 'Delayed' or type D ADRs are those that occur following prolonged use of a drug, usually for a chronic condition.
- Type E or 'end' of treatment reactions occur as a result of the discontinuation of a drug (e.g. β -blocker withdrawal induced rebound arrhythmia).
- Type F refers to the therapeutic 'failure' of the drug. This is typically associated with the introduction of another drug and concomitant interactions.

Post-marketing surveillance to detect and monitor ADRs: current state-of-the-art

Pharmacovigilance programs in many countries rely on the use of postmarketing surveillance studies. Several methods are used in postmarketing surveillance to investigate the occurrence of ADRs in large patient populations, including:

- spontaneous reporting systems [28]
- prospective cohort or case control studies [29]
- analyses of regional or national health insurance data
- record linkage databases and registries [30,31]

Spontaneous reporting to regulatory agencies, such as the US Food & Drug Administration's (FDA) Adverse Event Reporting System, which includes the Medical Products Reporting Program, MedWatch [32], and the UK's yellow card scheme operated by the Committee on Safety of Medicines [33] are typically the most common pharmacovigilance methods used to identify new or rare ADRs once drugs have been approved and are on the market.

Examples of some drugs that were withdrawn from the market due to reporting of serious adverse events are highlighted in Table 1.

However, spontaneous reporting systems have several limitations. Spontaneous reporting is limited by under-reporting. The true extent of under-reporting is not known although estimates range between 2–4% to 8–13% [20,34]. Another limitation of using spontaneous reporting to identify ADRs is the inconsistency inherent in the development of a specific ADR. In some cases, certain ADRs are sufficiently rare in the general population and develop rapidly after drug use, thus permitting the association of the ADR with the specific drug. In other cases, however, such as the well-known example of the development of valvular heart disease in young women who were taking appetite suppressants with phenteramine and fenfluramine [35,36], the ADR takes considerably longer to develop. If the ADR tends to be relatively common in the general population, this makes it more difficult to associate the ADR with the use of a new drug.

Other limitations of the use of spontaneous reporting include poor documentation and the apparent lack of association between the rates of spontaneous reporting and prescribing patterns [28].

Although record linkage databases have been in use in North America for a number of years, it is only in recent years that two databases have been developed in the UK: the General Practice Research Database (GPRD) [37] and the Medicines Monitoring Unit database [38].

Of the various methods of postmarketing drug surveillance, pharmacogenomics resembles therapeutic drug monitoring (TDM) most similarly [39]. Therefore, it is appropriate to briefly review the fundamental features of TDM.

Therapeutic drug monitoring

TDM is an established system of monitoring certain classes of drugs in patients based on the notion that plasma concentrations of a drug more accurately reflect toxicity or therapeutic

Table 1. Selected examples of drugs withdrawn from market due to serious ADRs.

Drug	Indication	ADRs	Year withdrawn
Baycol® (cerivastatin)	Cholesterol lowering	Rhabdomyolysis	2001
Propulsid® (cisapride)	GERD	Torsades de Pointes	2000
Rezulin® (troglitazone)	Diabetes	Liver failure	2000
Lotronex® (alosetron hydrochloride)	Irritable bowel syndrome	Ischemic colitis	2000
Seldane® (terfenadine)	Antihistamine	Torsades de Pointes	1998
Redux® (dexfenfluramine hydrochloride)	Appetite suppressant	Valvular heart disease	1997

ADR: Adverse drug reaction; GERD: Gastroesophageal reflux disease.

effects [40]. TDM is generally indicated for drugs with a narrow therapeutic margin, such as lithium, or drugs that appear to have an unpredictable dose–response relationship making it difficult to establish clinical efficacy, such as some tricyclic antidepressants (e.g., imipramine). TDM is also indicated in patients where underlying disease symptoms may mask possible drug-related toxicity, such as the administration of theophylline in chronic obstructive pulmonary disease (COPD), and in patients with impaired clearance mechanisms, such as patients with renal failure. Collection of TDM data is usually done by blood draws that are assayed for particular metabolites.

TDM has limitations, including patient non-compliance, incomplete adherence and variability of TDM between different laboratories, and cannot realistically be reliably employed for widespread clinical use [39,40]. More recently, several authors have proposed that pharmacogenomic profiling can be used as an adjunct to conventional TDM [39,41]. The next section will explore these proposals and evaluate the anticipated benefits and challenges that might emerge.

Prospects for pharmacogenomics approaches for pharmacosurveillance

Current research in pharmacogenomics is directed towards two primary goals:

- The identification of novel genetic targets associated with various diseases for the development of new therapeutic agents.
- The identification of specific genetic poly-

morphisms that are associated with responsiveness and/or adverse events to currently available drugs [42].

Pharmacogenomic-based research and development can be focused to identify genetic polymorphisms that are associated with either the ability to respond (efficacy) or with specific adverse events (i.e., safety). Although these two objectives frequently overlap, increasingly industry leaders and certain authors are focusing on the purported potential of pharmacogenomics to minimize or eliminate drug associated adverse events [18,43–45].

Although the science of pharmacogenomic profiling for the purposes of predicting ADR susceptibility is still in its infancy, several commonly cited examples of genetic polymorphisms known to be associated with drug ADRs are illustrated in Table 2. The best known example is the cytochrome P450 (CYP450) enzyme superfamily [46]. A significant number of therapeutic drugs are metabolized by the CYP450 system and the CYP2D6 and 2C polymorphisms have been a particular focus of interest [46]. This information has fueled the pharmaceutical industry's enthusiasm in performing prospective genotyping and phenotyping screening in clinical trials for compounds that are metabolized by these CYP isoforms [47–50]. Thus, the incentive to employ pharmacogenomic profiling towards identifying ADRs is strong. However, to date the evidence for the utility of this application of pharmacogenomics in clinical settings and how pharmacogenomic profiling can be used as a

Table 2. Selected examples of specific genetic polymorphisms known to be associated with certain ADRs.

Genetic polymorphism	Drug class	Examples of drug(s)	Reported adverse drug reaction	Ref.
TPMT	Antimetabolite chemotherapeutics	Mercaptopurine Azathiopurine	Myelotoxicity, leukopenia, death	[52]
NAT2	Antimycobacterial	Isoniazid	Peripheral neuropathy	[61,83]
	Vasodilator (antihypertensive)	Hydralazine	Drug-induced lupus, hypotension	
CYP2D6	Opioids	Codeine	Severe abdominal pain or no pain relief (depending on whether poor or ultra-rapid metabolizer)	[57-60,84]
	Tricyclic antidepressant	Desipramine	Cardiotoxicity, sudden death	
CYP2C9	Anticoagulant	Warfarin	Risk of bleeding	[53,54]

ADR: Adverse drug reaction; CYP: Cytochrome P450; NAT: N-acetyltransferase; TPMT: Thiopurine S-methyltransferase.

novel form of TDM is limited. A review of the pharmacogenomics literature suggests that many authors are optimistic about the potential for pharmacogenomic profiling for ADR susceptibility, yet actual proof of concept data are presently rather limited. One well known example is the use of genotyping or functional enzyme analysis of thiopurine methyltransferase (TPMT) in order to adjust the dose of chemotherapeutic agents, such as 6-mercaptopurine, in patients for whom the standard dose presents with severe hematologic and hepatic toxicity [51].

Other drugs that are considered potential candidates for pharmacogenomic testing for association with specific ADRs but are not yet in routine clinical use, include warfarin [52,53], phenytoin [54,55], codeine [56,57] and tricyclic antidepressants [58,59]. Interestingly, the criteria for their candidacy appear to be similar to those for conventional TDM, including the fact that these drugs show a narrow therapeutic margin [60]. Thus, the use of pharmacogenomic profiling for the identification of ADR susceptibility in pharmacovigilance has a number of methodological limitations at the present time.

Methodological, regulatory and ethical considerations

Several key methodological, regulatory and ethical issues remain to be resolved before the promise of pharmacogenomic profiling as a novel method of pharmacosurveillance for the prevention of ADRs can be realized. A review of the literature evaluating the potential of using

genotyping as a new form of TDM or as an adjunct to conventional TDM suggests that pharmacogenomic-based TDM has a number of shortcomings.

One consideration is the practical clinical relevance of pharmacogenomic screening. It is a well accepted tenet among pharmacologists and physicians that other factors, such as age, gender, underlying disease and drug–drug interactions all play important roles in understanding the variability of drug metabolism and therefore drug response and possible adverse events, in addition to genetic variation [61]. Pharmacogenomics conducted as TDM would provide some information but this would be of limited value. Another methodological concern centers on clinical validity and reliability of the molecular diagnostic tests that are developed. Other scientific challenges to the clinical use of pharmacogenomics that remain to be resolved include genotype–phenotype correlations, development of appropriate haplotype technology (which is still in its infancy), SNP profiling technology and the development of more economically feasible genotyping strategies.

The use of pharmacogenomics profiling to associate a specific ADR, hypersensitivity reaction (HSR) with exposure to the anti-HIV retroviral abacavir, has been proposed as a model example of using pharmacogenomics in the postapproval period [62]. Two studies demonstrated an association between the HLA B5701 polymorphism and HSR due to abacavir [63,64]. Sensitivity ranged from 72 to 78% in the prospective study by Mal-

lal *et al.* [63] and was 46% in the retrospective case-control study [64]. Both Mallal *et al.* [63] and Hetherington *et al.* [64] acknowledge the difficulties inherent in HLA testing with rather limited sensitivity. Indeed, the clinical utility of genotyping for this HLA association with abacavir-related HSR remains debatable [65].

The problems associated with achieving both the appropriate sensitivity and specificity in pharmacogenomic profiling diagnostics are not entirely insurmountable. Not only are there continuous technological improvements with genome SNP mapping techniques but analytical validation standards exist in industry [101,102].

However, other issues, both methodological and ethical, may be more difficult to resolve. Of note, limited functional and prevalence data exist regarding drug transporters and therapeutic targets. Realistically, in order for pharmacogenomics to be used for pharmacosurveillance, such as a TDM approach, it is necessary to integrate information related to drug-metabolizing enzymes, drug transporters and therapeutic targets, because these contribute to a drug's pharmacokinetics and pharmacodynamics.

There are also important considerations related to the multifactorial and polygenic nature of ADR susceptibility [66]. It is interesting that the genetic polymorphisms associated with specific ADRs that have been characterized the best tend to be those related to type A ADRs, such as the case of TPMT [66]. It has been shown to be much more difficult to use pharmacogenomic profiling approaches to identify and predict other categories of ADRs, such as type B, C and D reactions [66].

An important scientific challenge, at least initially, with a concomitant regulatory and ethical concern arises from the statistical requirement of sufficient power needed to associate a genotype definitively with a particular adverse event. At the present time, association studies require a large number of patients in order to achieve adequate statistical power [67-70]. Generally, the purpose of surveillance during the postapproval period is to determine serious ADRs from newly approved drugs that result in the withdrawal of the drug from the market. However, a genotyping diagnostic test cannot meet the validation clinical specificity and sensitivity standards without the sufficient sample size. This may entail exposing a large number of patients to a given therapeutic agent and potentially to a serious ADR.

Some authors have suggested that pharmacogenomic profiling raises less ethical concerns than

other areas of genetic testing because, with SNP mapping technology, it is possible to identify the polymorphism of interest for drug-responsiveness or an ADR only and avoid relating it to disease [9,44,62,71]. However, realistically there is and will be significant overlap between polymorphism-ADR associations and disease susceptibility-related polymorphisms [73,74]. For example, the association of the apolipoprotein E (ApoE) polymorphism with response to lipid-lowering drugs is well known [75-78]. At the same time, ApoE is predictive of increased risk of Alzheimer's disease [3,76]. Thus, it is quite possible that pharmacogenomic-based diagnostic testing may inadvertently result in information regarding disease susceptibility. This, in turn, would lead to a number of ethical problems, such as those related to privacy and confidentiality, insurability, consent etc., usually associated with other forms of genetic testing.

Recently, the development of databases of genetic profiles associated with ADRs has been proposed [44,79]. The growing interest in the development of databases associating ADRs and/or drug-responsiveness with genetic polymorphisms presents with ethical concerns that are particularly cogent for the subject of this article. If pharmacogenomics is to be useful as an approach to surveillance in the postapproval period, genome banks of samples for retrospective analysis and databases linking polymorphisms with suspected ADRs and other pertinent information will become increasingly necessary. Several genomic repositories and databases are already in operation including Genbank®, dbSNP and PharmGKB [80-82].

A number of ethicists and other commentators argue that a possible solution to the problems associated with potential misuse of information, breach of confidentiality and stigmatization related to repositories and databases is to anonymize samples that are collected by removing all patient identification information or to restrict the data to a select number of healthcare professionals [83,84]. However, such an approach would likely defeat the purpose of pharmacogenomic databases for postmarketing TDM purposes. Thus, there is an urgent need at local, national and international levels for the regulatory and legislative adoption of standards to ensure the legitimate use of pharmacogenomic data.

Another issue that presents with ethical quandaries is the potential use of pharmacogenomics to 'rescue' drugs that have previously been withdrawn from the market. Although the use of

pharmacogenomic profiling to determine genetically-based ADRs associated with a particular drug may, in some cases, provide sufficient safety-related information, the difficulties with test validity, sensitivity and specificity mentioned earlier especially if these are combined with economic considerations by industry, might lead to the reintroduction of certain drugs with disastrous results.

In light of these ethical and social concerns, an important consideration is whether pharmacogenomics will have a truly significant impact on reduction of ADRs as some believe. As previously mentioned, pharmacogenomics might not significantly impact all classes of ADRs. Indeed, one author estimates that in ~ 50% of cases, pharmacogenomics-based approaches to therapeutics will not be of any important consequence, because those cases where successful outcomes are achieved are due mainly to high penetrance and these account for a considerably smaller number of cases [85].

Expert opinion

Pharmacogenomic profiling appears promising as an approach to drug surveillance in the postapproval period. However, current pharmacogenomic studies are hampered by methodological and study design constraints. In addition, a number of ethical and regulatory issues remain to be resolved. In order for pharmacogenomics to be applied appropriately towards the goal of reducing ADRs, there is a dire need to advance

the science of pharmacogenomics simultaneously on several fronts.

To date, the advances in pharmacogenomics have come primarily from studies of monogenic polymorphisms. More attention to polygenic expressed traits is needed in order for this field to make a contribution that is consistent with the complexity of clinical reality.

More emphasis needs to be placed on refining association studies and developing new clinical trial design strategies as well as technologies. Future studies should also include appropriate pharmacoepidemiological criteria and methods to evaluate the utility of pharmacogenomic applications in postmarketing surveillance.

At the same time, the ethical and regulatory issues, especially those pertinent to the use of databases, need to be resolved.

Outlook

The potential applications of pharmacogenomics as a tool in the drug postapproval process to confront the problem of ADRs appear promising, provided that the methodological, study design and ethical considerations are dealt with and resolved. Within the next 5–10 years, the necessary technology for the determination of true haplotypes is expected to advance. This should resolve some of the problems associated with the inherent limitations of current SNP analysis technology.

A priority for future research will, as a necessity, include the development of better epidemiological and study design criteria and standards to improve the quality of pharmacogenomic studies. However, a number of scientific, regulatory and ethical challenges to the implementation of pharmacogenomic profiling into pharmacoepidemiology remain. These challenges need to be resolved before the opportunities for pharmacogenomics at all levels of healthcare, including research and development and postmarketing surveillance, can be fully realized.

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Highlights

- ADRs are a major worldwide problem for the pharmaceutical industry and the provision of healthcare.
- Increasingly, a substantial subset of pharmacogenomics research is directed towards the potential reduction in ADRs.
- Several authors and industry leaders are advocating the use of pharmacogenomic profiling as a form of surveillance during the postapproval period as well as during the phases of pre-approval clinical drug trials.
- However, the question of whether pharmacogenomics might be feasible as a pharmacovigilance tool in postmarketing surveillance has not been well addressed.
- The application of pharmacogenomic profiling presents with several methodological and ethical challenges that are critically analyzed.

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