

Personalized Medicine and the Future of Drug Safety

By Amalia M. Issa, MPH, PhD

Several recent high profile cases of popular prescription drugs that were withdrawn from the market following serious adverse events (1,2) have highlighted the need for improved drug safety. In September 2004, the non-steroidal anti-inflammatory COX -2 inhibitor Vioxx® was withdrawn from the market in response to the results of a post-marketing study that demonstrated a significantly increased risk of developing cardiovascular episodes in patients who had been taking the drug for more than 18 months. (3) Valdecoxib (Bextra ®), a similar COX -2 inhibitor followed suit and was also withdrawn in April 2005.

Despite the public perception that drug withdrawals may be increasing, we found that only about 1% of drugs that were approved since 1993, the year that the Prescription Drug User Fees Act (PDUFA) came into effect, were withdrawn from the market due to safety concerns (unpublished results). Nevertheless, adverse events appear to be affecting more people, and drug safety is increasingly becoming a major issue on the national health agenda. Indeed, drug safety was the topic of discussion of several sessions at the recent Annual Meeting of the American Public Health Association. (4-6)

An important current trend in healthcare is the move towards a model of personalized medicine that incorporates genetic information, and this represents one promising innovation to improving drug safety. Personalized medicine can be broadly defined as an approach that involves incorporating diagnostic and therapeutic interventions based on integrating individual genotyping with family and clinical histories. A key component of personalized medicine is translating the science of pharmacogenomics into clinical practice. Pharmacogenomics is increasingly seen as holding the potential for tailoring prescriptions to defined sub-populations and possibly individuals based on genetic make-up, and therefore improving the effectiveness and safety of drugs.

This paper addresses the potential of personalized medicine for improving drug safety as well as some of the challenges in implementing it into clinical practice.

A Brief History of Pharmacogenetics and Pharmacogenomics

The capacity for genetic differences to affect response to the biochemical environment has been known for over 100 years. Historically, one of the first indications of genetic polymorphism in drug metabolism was suggested by studies on alkaptonuria in 1902. (7) Alkaptonuria is a disorder in which the enzyme homogentisate oxidase does not correctly process its intended target substrate, homogentisic acid leading to a build up of that substrate. Alkaptonuria is usually asymptomatic, but can lead to arthritis.

A curious observation of hemolysis among African-American soldiers in response to taking the antimalarial drug primaquine provided evidence of genetic variation in response to drug ingestion when further studies demonstrated that this primaquine – induced hemolysis was due to a genetic deficiency of the enzyme glucose – 6- phosphate

dehydrogenase (G-6-PD). (8) The significance of pharmacogenetics to the clinical care of patients was shown by Kalow and Gunn (9) who observed an excessive neuromuscular blockade and longer-lasting apnea in some patients who had been administered the neuromuscular blocking agent, succinylcholine, as part of undergoing electroconvulsive therapy. These and other observations established the early foundation of the field of pharmacogenetics.

The more recently coined term, “pharmacogenomics” is more encompassing describing the impact of genomic information on the drug discovery process. Therefore, pharmacogenomics includes identifying candidate genes and polymorphisms, correlation of polymorphisms with therapies, prediction of drug response and clinical outcomes, reduction in adverse events (side effects), and selection and dosing of drugs based on genotype. (10) Thus, the prediction of polymorphisms has implications for reducing adverse events, improving the design of rational drug development, and eventual drug prescription.

Some of the anticipated long-term benefits of pharmacogenomics include the potential for “personalized” or “customized” prescriptions, improved patient compliance, reduction or elimination of certain adverse events and the reduction in cost of disease management. The potential applications for genotyping for pharmacogenomics purposes are diverse and are primarily driven by three requirements (10-13): First, the need to determine the safety and efficacy of an experimental new drug prior to approval; second, the need to establish an individual's genetic predisposition to a disease state; and, third, the need to protect patients against possible adverse drug reactions by identifying poor metabolizers at the initiation of drug therapy. The use of genotyping in the identification of poor metabolizers prior to the initiation of drug therapy is an appealing emerging opportunity for pharmacogenomics. Physicians may choose to screen their patients before administering certain drugs.

The Potential Benefits of Pharmacogenomics for Improving the Science of Adverse Drug Events

The interest in using pharmacogenomics to improve drug development efforts is presently largely driven by economic incentives. Many of the major revenue –generating drugs for the industry are either off patent or approaching patent expiration. Notable examples in the past few years include Ely Lilly's Prozac and AstraZeneca's Prilosec. (14) Pharmacogenomics is expected to shift the focus of the pharmaceutical industry from the conventional “blockbuster” approach to drugs that target sub-populations. (15) Current research in pharmacogenomics is directed towards two primary goals: First, the identification of novel genetic targets associated with various diseases for the development of new therapeutic agents; and second, the identification of specific genetic polymorphisms that are associated with responsiveness and/or adverse events to currently available drugs. (13,16)

Pharmacogenomic - based R & D 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. (13,17-18)

Although the science of pharmacogenomic profiling for the purposes of predicting ADR susceptibility is still in its infancy, there are several examples of genetic polymorphisms known to be associated with drug ADRs. (19) The best known example is the cytochrome P-450 (CYP450) enzyme superfamily. (20) A significant number of therapeutic drugs are metabolized by the CYP-450 system and the CYP-2D6 and 2C polymorphisms have been a particular focus of interest. (20) 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. (16,21)

In a recent study examining trends and characteristics of prescription drugs that were withdrawn between 1993 and 2005, we found that about one-quarter of drugs (unpublished results) that were withdrawn were due to adverse outcomes that may be associated with genetic variability according to suggestive evidence in the literature. (22,23)

The withdrawal of cerivastatin (Baycol®) in August 2001, may be a particularly cogent example. Cerivastatin, a 3-hydroxy-3 methylglutaryl co-enzyme A (HMG -CoA) reductase inhibitor (a statin), was withdrawn from the market following reports of over 500 cases of rhabdomyolysis, with some 100 of these cases being fatal. (24-26) About 50% of the rhabdomyolysis cases associated with cerivastatin involved concomitant use of the lipid-lowering fibrinolytic gemfibrozil. Subsequent to the withdrawal of cerivastatin, concerns were raised about other statins. (27, 28) However, there is evidence of differences in the risk of rhabdomyolysis occurrence among the different statins. (29) For instance, pravastatin and fluvastatin appear to be the least likely to result in rhabdomyolysis, and it has been suggested that, in contrast to cerivastatin, this may be due to their apparent lack of metabolism specifically by the cytochrome P450 CYP3A4 isoenzyme. (27) Moreover, the apparent clinically important interaction between gemfibrozil and cerivastatin suggested by the pharmacokinetic studies may be, at least partly, related to the inhibition by gemfibrozil of CYP2C8 (30,31), a substrate which is also thought to play a role in the metabolism of cerivastatin. Thus, although limited, evidence is building to suggest the utility of pharmacogenomics to predict and thereby potentially avoid certain types of adverse events. Pharmacogenomics also has the potential to improve drug safety by detecting potential adverse events at an earlier stage in the drug development process. (10,32,33)

However this potential is not without challenges, particularly with respect to translation on a wider scale into clinical practice. Key among these challenges is potential market disincentives. For instance, an analysis by Hill et al. (34) on products for hyperlipidemia suggested that pharmacogenomic drug development would likely “grow the total market” but that revenues for the statins would be reduced as the more novel pharmacogenomic-based drugs captured some of the sales. For their analysis these authors started with the \$9.7 billion hyperlipidemia market in 2001 of which \$9.3 billion was for the statins, and

projected that the total hyperlipidemia market would grow to about \$18.5 billion by 2010, but that statin revenues would only grow to \$15 billion. (34) According to the model by Hill et al. (34), novel more-pharmacogenomic-based drugs would capture about \$3 billion in sales, but no one new therapeutic is likely to be a blockbuster in sales.

On the other hand, it is conceivable that there may be public demand for genetic profiling tests to predict adverse reactions or response to drugs and that some consumers may want to pay for these tests.

It is well known that the current era of managed care in the U.S. health system has imposed time and commercial pressures on the health care community. Although managed care has generally been favorably disposed towards diagnostic testing and preventative screening, the additional testing associated with pharmacogenomics-based therapeutics may overwhelm the medical community with a new set of challenges. Clinical application of most genetic tests requires considerable interpretation and such an added dimension of complexity to routine drug prescribing may not only require further education on the part of providers, but also increased costs for health plans. (35) It is uncertain at this time whether managed care will embrace pharmacogenomics and the associated costs for health plans, particularly since, as mentioned above, pharmacogenomics drugs are likely to be a generation of very expensive pharmaceuticals.

Pharmacogenomics will likely have a profound impact on reimbursement decisions and consequently access to pharmacogenomics drugs and accompanying genetic profiling tests by patients. As mentioned above, pharmacogenomics will introduce new costs including those related to genetic profiling, data collection and analysis, and monitoring services. Given the current climate in the United States surrounding the debates over drug pricing, market acceptance of pharmacogenomics drugs will likely be predicated upon a strong demonstration of safety, efficacy and utility of these new pharmacogenomics-based pharmaceuticals. Thus, pharmaceuticals developed using pharmacogenomics technologies may meet with market resistance in the absence of significant clinical utility benefits to offset the inevitable price increases.

CONCLUSION

It may be a decade or so before pharmacogenomic drugs and accompanying genetic profiling tests become routinely available. Nevertheless, it is important to undertake an analysis of some of the potential implications for the market and for policy. The anticipated future market entry of pharmacogenomics-based pharmaceuticals will likely add several new dimensions to regulatory and health care policy issues including long-standing ones such as genetic exceptionalism, market acceptance and access by patients. The use of pharmacogenomics in drug development holds some promise. However, despite the advances made to date, pharmacogenomics remains laden with scientific, technical, regulatory and economic concerns and uncertainties. The key challenge at this time is the development of policy under the purview of uncertainty on a number of different fronts.

References

1. Wadman M. Drug Safety Special: The Safety Catch," Nature 434: 554-556, 2005.
2. Waxman HA The Lessons of Vioxx - Drug Safety and Sales. New England Journal of Medicine 352: 2576-2578,2005
3. Singh, D. Merck withdraws arthritis drug worldwide. BMJ 329: 816, 2005.
4. Eilers RP. "After Vioxx: Whither drug safety in the U.S. ?" American Public Health Association Annual Meeting, # 120486, Philadelphia , PA , December 14, 2005 .
5. Feinberg JL. "Novel pharmacist interventions to improve medication safety: Using clinical informatics to improve patient safety at the medication monitoring stage," American Public Health Association Annual Meeting, # 106502, Philadelphia , PA , December 13, 2005 .
6. Field R. Post-market drug surveillance: Options for reform. American Public Health Association Annual Meeting, #105982, Philadelphia , PA , December 14, 2005.
7. Garrod 1902
8. Carsen et al. 1956
9. Kalow and Gunn, 1957
10. Issa, A.M. Perspectives in pharmacogenomic profiling in the drug development process. Nature Rev. Drug Discov . 1: 300-308, 2002.
11. Evans WE and Relling MV. Pharmacogenomics: Translating functional genomics into rational therapeutics. Science 286: 487 – 491, 1999.
12. Arledge T, Freeman A, Arbuckle J, Mosteller M, Manasco P. Applications of pharmacogenetics to drug development: The Galxo Wellcome experience. Drug Metab. Rev . 32: 387 – 394, 2000.
13. Kurth JH. Pharmacogenomics: future promise of a tool for identifying patients at risk. Drug Info J . 34: 223-227, 2000.
14. Robbins-Roth, C. From Alchemy to IPO: The Business of Biotechnology , pp. 73-78, Perseus Publishing, Cambridge, MA, 2003.
15. Roses AD. Genome-based pharmacogenetics and the pharmaceutical industry. Nature Rev. Drug Discov. 1, 541-549, 2002.

16. Shi MM, Bleavins MR, and de la Iglesia FA. Pharmacogenetic application in drug development and clinical trials. *Drug Metabolism & Disposition* 29, 591-595, 2001.
17. Primohamed M and Park BK. Genetic susceptibility to adverse drug reactions. *Trends Pharmacol. Sci.* 22, 298- 305, 2001.
18. Güzey C. and Spigset O. Genotyping of drug targets: a method to predict adverse drug reactions? *Drug Safety* 25, 553-560, 2002.
19. Ingelman-Sundberg M. Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy. *Philosophical Transactions of The Royal Society B Biological Sciences* 360: 1460, 2005.
20. Rodrigues AD and Rushmore TH. Cytochrome P450 pharmacogenetics in drug development: In vitro studies and clinical consequences. *Curr. Drug Metab.* 3, 289-309, 2002.
21. Rogers JF, Nafziger AN, and Bertino JS Jr. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450-metabolized drugs. *Am. J. Med.* 113: 746-750, 2002.
22. Bernard, 2003
23. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N. Engl. J. Med.* 352: 2211-21, 2005.
24. Farmer JA. Learning from the cerivastatin experience. *Lancet* 358: 1383-85, 2001.
25. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N. Engl. J. Med.* 2002; 346: 539-40, 2005.
26. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann. Pharmacother.* 36: 288-95, 2002.
27. Sica DA, Gehr TW. Rhabdomyolysis and statin therapy: relevance to the elderly. *Am. J. Geriatr. Cardiology* 11: 48-55, 2002.
28. Grundy SM. The issue of statin safety: Where do we stand? *Circulation* 111: 3016-19, 2005.
29. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 292: 2585-2590, 2004.
30. Backman JT, Kyrklund C, Neuvonen M, Neuvonen PJ. *Clin. Pharmacol. Ther.* 72: 685-691, 2002

31. Prueksaritanont T, Zhao JJ, Ma B, Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J. Pharmacol. Exp. Ther* 301: 1042-51, 2002.
32. Phillips KA, Veenstra DL, Oren E, Lee JK, and Sadee W. "Potential Role of pharmacogenomics in reducing adverse drug reactions: A systematic review. *JAMA* 286: 2270-2279, 2001.
33. Issa, A.M. Pharmacogenomic profiling in post-marketing surveillance: Prospects and challenges *Pharmacogenomics* 4: 647-655, 2003.
34. Hill R, Frankel B. and Kurdikar D. Modeling pharmacogenomics. *In Vivo* November, 77-79, 2001.
35. Mahowald, M. *Genetics in the Clinic: Ethical and Social Implications for Primary Care*, 2001.

About the Author: Amalia M. Issa, MPH, PhD , is Director of the Program in Personalized Medicine and Targeted Therapeutics, Abramson Family Center For The Future of Health and Associate Professor of Technology at the University of Houston.