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‘Generic to genetic’ transition in cardiovascular and neuropsychiatric drugs: opportunity for personalized medicine

Jorge Duconge and
University of Puerto Rico Medical Sciences Campus, School of Pharmacy, San Juan, PR 00936-5067, USA

Gualberto Ruaño
Genetics Research Center, Hartford Hospital & Genomas Inc., 67 Jefferson Street, Hartford, CT 06106, USA

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The challenge of generic transition

One of the common challenges in pharmacogenetics 10 years ago was a perceived conflict between the marketing model of the pharmaceutical industry based on blockbuster medications and the clinical model of personalized medicine based on individualized prescription. Now this conflict has nearly vanished, as the blockbuster brands are yesterday’s products, and the marketplace has a cornucopia of generics. The healthcare sectors embracing pharmacogenetics are now the pharmacy management and managed care constituencies. For every dollar spent on branded products, only 10–20 cents is required to buy a generic equivalent. The resulting spread of 80 cents is there for distribution, and there is an economic incentive for pharmacogenetics business to grab it.

On the other hand, despite the growing interest of pharmaceutical industry and payers in pharmacogenomics, following the successful and profitable case of Roche’s Herceptin (trastuzumab) and its diagnostic test by Dako (Glostrup, Denmark) [1], there is still the perception that relatively lower incentives and, therefore, less enthusiasm exist for investing in the development of pharmacogenetic diagnostics for generic drugs, as current reimbursement systems are accustomed to supporting a low margin market for such tests, and there will be no single beneficiary.

Approximately US$100 billion in annual sales of brand name drug products will be at stake due to emerging generic competition from 2011 to 2015, representing approximately one-

Author for correspondence: Tel.: +1 860 545 3773, Fax: +1 860 545 4575, gruano@harthosp.org.

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third of the annual spending on all prescriptions in the USA, according to IMS Health (CT, USA) data [101]. With patent expiration dates for several patents already lapsed or approaching for various blockbuster cardiovascular and neuropsychiatric pharmaceuticals (Supplementary Table 1, see www.futuremedicine.com/doi/suppl/10.2217/pgs.12.75), including two of the ten best-selling drugs (i.e., Lipitor® [Pfizer, NY, USA] in November 2011 and Plavix® [Bristol-Myers Squibb/Sanofi Pharmaceuticals partnership (NJ, USA)] in May 2012) [102,103], we firmly believe that the marketplace for DNA typing of functional variants clinically associated with their responsiveness or adverse events predictions is looming large. This is because generic transition will trigger formulary changes, therapeutic switches and immediate price drops, which are often accompanied by a larger number of prescriptions for the drug, meaning more people being pushed to use generic versions and hence a wider range of patients receiving the drug and, obviously, more chances for substantial intersubject variability in medical outcomes and dosage requirements. This scenario definitely calls for a need to refine the implementation of personalized healthcare strategies, particularly in the clinical management of individual patients' drug therapy. In this context, pharmaco-genetics/-genomics has the potential to significantly enhance the predictability and further clinical utility of such decision support tools for DNA-guided personalized prescriptions in clinical settings.

Cardiovascular prescription drugs

The case of the drug clopidogrel (Plavix) showcases this situation well. This antiplatelet drug is Bristol-Myers Squibb's best-selling product, with worldwide net sales of US$1.5 billion. Clopidogrel has a proven record of thrombosis prevention in different populations worldwide [2]. In 2002, the American College of Cardiology (DC, USA) and American Heart Association (TX, USA; ACC/AHA) designated it the preferred P2RY12-receptor antagonist, and their recent guidelines recommend it for treating acute coronary syndrome or myocardial infarction with ST-segment elevation [3,4]. Upon its patent expiry in May 2012, Plavix transitioned to generic clopidogrel, which caused the price to drop well below that of Effient® (Eli Lilly, IN, USA) and Brilinta® (AstraZeneca, London, UK). Generic status is expected to reduce the cost for clopidogrel (75 mg daily dose) from US$5 to less than US$1 per dose, a saving of nearly US$1500 per patient per year.

Early on, clopidogrel resistance has been described by others as a phenomenon affecting as many as 30–40% of patients receiving the medicine [2,5]. Although many patients qualify for clopidogrel therapy based on medical needs, they usually lack insurance to pay for the drug. However, the generic transition in 2012 will increase the number of eligible patients and, therefore, the amount of nonresponders is expected to skyrocket. It is becoming increasingly clear that a pharmacogenetic test for functional *CYP2C19* polymorphisms (e.g., *CYP2C19*2* and **3*), and perhaps for the *PON1* Q192R variant [6–10], has the capacity to identify responders versus nonresponders in patients undergoing percutaneous coronary intervention. Companion genotyping at $200–300 would result in an annual cost of ~US $600 for clopidogrel, compared with ~US$2000 per year for its branded competitors. Beyond the significant monetary advantage, clopidogrel is also suitable for outpatient management.

On the other hand, Jackevicius *et al.* projected that the ratio of the price of generic atorvastatin to that of Lipitor will be 0.82 at the time of market entry of the generic and 0.49 after the 6-month exclusivity period that is granted to the first generic product [11]. At least one generic atorvastatin is now available (from Ranbaxy Laboratories Ltd, Gurgaon, India). As of 2011, Lipitor had annual sales of US$7 billion in the USA, according to medical data provider IMS Health [101]. The overall cost savings from the availability of generic atorvastatin are projected to reach US$4.5 billion annually by 2014, equivalent to 23% of

total expenditures on statins in that year [11]. Out-of-pocket costs of the generic version of Lipitor will be reduced to as little as US$4 each month. Today, it is possible to predict risk of statin-induced neuromyopathy, based on a patient's combinatorial genotyping test for 50 genes (statin-induced neuromyopathy [SINM] PhyzioType™ [Genomas, Inc., CT, USA]) [12–15]. Over the next few years, some other statin-containing 'blockbuster' products – with total annual sales above US$8 billion – will lose their patents (i.e., Lescol®/Lescol XL [Novartis, Basel, Switzerland] in June 2012; Vytorin® [Merck/Schering-Plough (NJ, USA)] in March 2014 and Crestor® [AstraZeneca] in January 2016) and their generic products are expected to become increasingly available.

Neuropsychiatric prescription drugs

Olanzapine (Zyprexa®, Eli Lilly), an atypical antipsychotic agent, is used to treat schizophrenia and related psychotic disorders. Previous studies have identified genetic risk factors for olanzapine-induced weight gain that may result in metabolic syndrome. In addition, by using the psychotropic-induced metabolic symptoms (PIMS) PhyzioType™ (Genomas, Inc.) we can predict risk of psychotropic-induced metabolic syndrome based on a patient's combinatorial genotype for 50 genes [16,17], a test that has been demonstrated to be useful in decision-making support for patients to be treated with Risperdal® (Janssen Pharmaceutica, Antwerp, Belgium; resperidone) and Zyprexa (olanzapine). In 2008, worldwide Zyprexa sales reached US$4.7 billion. Cost–effectiveness analyses have indicated that olanzapine has the lowest mean annual direct healthcare cost (US$8544). Olanzapine has been found to be the dominant choice in terms of incremental cost–effectiveness per quality-adjusted life years gained (0.733 vs 0.719) [18]. The utilization of generic olanzapine is expected to result in lower mean total healthcare costs from the perspective of payers in the US healthcare system. The long-standing debate about relative economic benefits of first-versus second-generation antipsychotics has become less relevant for payers, who may have little incentive to use first-generation antipsychotics following patent expiry and availability of second-generation antipsychotics in generic form (e.g., olanzapine generic since October 2011; ziprasidone generic since January 2010; and quetiapine generic since March 2012) and lower cost [18].

Lexapro® (Forest Pharmaceuticals, NY, USA; US$2.9 billion in annual sales [101]) was the last big selective serotonin-reuptake inhibitor (SSRI) to go generic in March 2012, and a generic version is now manufactured by Teva (Peteh Tikva, Israel). Once costs drop, practitioners will lean towards using escitalopram instead of citalopram, especially in the elderly or patients taking *CYP2C19* inhibitors (omeprazole, ethinyl estradiol and so on), because escitalopram appears less likely to cause QT prolongation at usual doses than citalopram. Other brand-name antidepressants whose patents will expire in the near future are Effexor® XR (venlafaxine extended-release; Wyeth [NJ, USA], in September 2017) and Cymbalta (duloxetine; Eli Lilly, in June 2013). Together, their total annual sales amounted to more than US$5 billion [101]. A generic version of Venlafaxine extended-release capsule was approved and launched after settlement with Teva.

A twist in the tale: the opportunity

Over the last 3 years and until 2014, some brand-name drugs with more than US$66 billion in annual sales have lost or are expected to lose patent protection. Some companies are taking aggressive steps to help patients afford innovative products that address true unmet need, and the ability of genetic screening to make generic drugs work better at an individual level will feature prominently in such an endeavor. As part of this global challenge, pharmacy benefit manager Medco Health Solutions Inc. (NJ, USA) launched the 'Genetics for Generics' Program in 2009–2010 for optimizing savings by dispensing generic drugs

such as clopidogrel and statins with the aid of genetic tests [104]. According to internal reports, up to 18% of spending increases were projected for the period spanning 2009–2011. With the Genetics for Generics Program, Medco (now merged with Express Scripts, MO, USA) was seeking to incur savings during a period when numerous brand name drugs are expected to go off patent [104,105]. Given the high rate of failure for initial prescriptions of drugs, pharmacy benefit manager involvement in promoting DNA-guided personalized medicine for generics at the community level seems to be a logical step in the right direction. The major incentive is to ensure that medicines can be prescribed correctly the first time so that money is not wasted due to empirical trial and error approaches. Although not included in the cardiovascular or neuropsychiatric drug classes, other brand-name drug products going off patent soon, with a well-known genetic test, are the antiretroviral Ziagen® (GlaxoSmithKline, London UK) in June 2012 (generic name: abacavir; genetic test: *HLA-B*5701* Screening for Hypersensitivity to Abacavir); and OxyContin (Purdue Pharma, CT, USA) in April 2013 (generic name: oxycodone extended-release tablet; genetic test: *CYP2D6*).

Conclusion

Certainly, the lack of substantial clinical data proving the cost–effectiveness and clinical utility of genetic tests have prevented practitioners from fully embracing DNA-guided personalized healthcare strategies for their patients. However, those who are believers in the personalized medicine paradigm are hoping that some ongoing clinical trials in this regard will help drive full adoption of certain genetic tests in the near future. The opportunity to reduce healthcare costs and improve everyday clinical practice using pharmacogenomic-guided pharmacotherapy is real, particularly in circumstances where inappropriate treatment can be prevented [19,20]. The fundamental idea behind DNA-guided personalized medicine is to combine our increased understanding of how genetic biomarkers correlate to medical outcomes with state-of-the-art molecular DNA profiling to create diagnostic, prognostic and therapeutic strategies precisely tailored to each patient's requirements. Ultimately, this approach should ensure that patients get the right treatment at the right dose at the right time, minimizing chances for adverse events and maximizing efficacy of drug therapies. Undoubtedly, significant challenges lie ahead. However, expectations must be realistic. Although implementation of the DNA-guided personalized medicine paradigm will not happen tomorrow, we firmly believe that transition to a generic marketplace will speed up and, eventually, streamline the process. To this end, new regulatory guidelines have to be steered by multidisciplinary, global consortia including leaders from academia, clinical practice, industry and government that come up with proposals for healthcare stakeholders and public consultation. Such a dialog will be critical to the DNA-guided personalized medicine enterprise in the pursuit of an optimal use of generics.

The generic to genetic transition provides an opportunity to leapfrog health standards in global populations to areas of medical need with potential disparities of care, notably including cardiovascular disease and mental illness. The generic to genetic transition also poses a great resource for translational clinical science in global populations to develop personalized healthcare systems, including diagnostics and information technology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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