Health Policy and Technology (2014) 3, 314–324

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/hlpt

Economic evaluation of the use of a pharmacogenetic diagnostic test in schizophrenia ☆

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Available online 19 August 2014

KEYWORDS
Pharmacogenetics;
Economic evaluation;
Schizophrenia;
Diagnostic tests;
Cost effectiveness;
Stratified medicine

Abstract
Objectives: The promise of personalized medicine has been difficult to realize due to a number of barriers to its development, including uncertainty regarding clinical utility and economic value. We aimed to provide an estimation of the cost-effectiveness of the use of a pharmacogenetic diagnostic test for Cytochrome P450 (CYP450) in schizophrenia used to adjust dosing prior to risperidone initiation, relative to traditional dosing patterns of risperidone in UK.
Methods: A deterministic decision model was developed to compare the health gain and costs of a patient stratification strategy versus traditional dosing. The time horizon of the model is two years, which consists of 24 cycles of one month. Input parameters were taken from the literature. Influential parameters were identified through sensitivity and scenario analyses.
Results: The patient stratification strategy improved health compared to the traditional dosing scheme, at an additional cost of £2059/patient. Varying key parameters of the model showed that the results were most sensitive to the assumptions regarding costs and health utility of patients who experienced treatment failure and the accuracy of the test. The price of the drug had the least influence on the results.
Conclusions: This study suggests that testing for CYP450 polymorphisms prior to treatment with risperidone to allow dose adjustment will most likely be cost-effective. Potential future research for the assessment of companion diagnostics and possible approaches to dealing with the challenging evidence generation in this growing field are discussed.

☆A travel grant was awarded by the Spanish Association of Health Economics (AES) to Juan Carlos Rejon to present and discuss preliminary findings in the XXXIII edition of their annual congress in Santander (Spain) in June 2013.

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http://dx.doi.org/10.1016/j.hlpt.2014.08.004
2211-8837/

Introduction

Personalized medicine is a field of health care that is attracting the attention of the pharmaceutical industry, governments and their reimbursement bodies, physicians and patients. The promise of a tailored therapy, the right dose to the right patient, has placed a lot of interest and expectations on this area of research. Efforts are being made to support such a hopeful prospect by generating evidence, both clinical and economic [1]. Economic considerations are key in the development of health technologies, especially in times of scarce resources. Despite these efforts, there is still a lack of cost-effectiveness evidence to support the uptake of companion diagnostics in medical practice [2]. There are a number of companion diagnostics required or recommended by the US FDA in different disease areas, and many more are in different stages of development, constituting an increasingly growing market [3]. In this article, as a means of an example, we study the case of personalized medicine in the field of mental health.

Neuropsychiatric disorders are a major cause of disability among the youth population aged 10–24 years worldwide. Up to 45% of total years of life with disability (YLDs) worldwide are caused by this group of diseases, followed by unintentional injuries (12% of YLDs) and even beyond the 10% of YLDs caused by infectious and parasitic diseases [4]. Neuropsychiatric disorders include schizophrenia, a disease which leads to a decrease in quality of life and also a reduction in length of life. According to estimates from the WHO [5], the mortality risk among schizophrenic patients is 50% higher than in the general population. Furthermore, schizophrenia has considerable economic consequences for individuals and societies worldwide, which is reflected not only in a loss in productivity but also in the high financial burden caused by care for this group of patients [6].

The optimization of a pharmacotherapy is a key component of disease management in schizophrenia. Compliance remains an unresolved issue in the treatment of schizophrenia [7]. For example, more than 35% of patients showed problems relating to compliance during the very early first stages of the initiation of a pharmacological treatment and only 25% remained fully compliant within 2 years [8]. In the Clinical Antipsychotic Trial of Intervention (CATIE) trial, which is the most recent effort to observe real-life outcomes in clinical practice, 74% of patients (n=1493) experienced treatment failure under their medication before 18 months [9]. The reasons for this include cognitive dysfunction, negative symptoms such as apathy and defects in attention control [10] and drug-related side effects, among others [11,12]. A possible approach to tackle these problems could be the use of long-acting therapy as proposed by Nasrallah [7]. Alternatively, rather than only focusing on a change in the form of treatment, another option would be the use of a test that allows stratification of patients for an optimal drug choice or dose which would avoid side effects and ultimately improve health outcomes [13].

Risperidone is among the treatment options listed by the NICE for first-line pharmacotherapy of schizophrenia patients [14]. In the NHS, treatment decisions for these patients are determined by the side effect profile of the pharmacotherapy options, in addition to the attitudes of the care provider and the patient. Risperidone is mainly metabolized through the CYP2D6 enzyme. The genotype of this enzyme determines to a great extent the plasma levels of the active metabolite of risperidone [15], which is an important determinant for predicting adverse drug reactions [16]. Therefore, a test that can be used to genotype for CYP2D6 and, consequently, predict the likelihood of each individual patient to suffer side effects with risperidone provides valuable information at the point of prescription.

Classification of patients into four classes is possible according to their phenotype of CYP2D6: poor metabolisers (PMs), in which both alleles of the gene are inactivated forms; intermediate metabolisers (IMs), with two alleles encoding a reduced activity or one null allele and the other one encoding reduced-activity; extensive metabolisers (EMs), with a minimum of one functional allele; and ultrarapid metabolisers (UMs), with an excessive activity of the enzyme due to the presence of several [3-13] functional copies of the active allele [17-19]. PMs should receive ~50% of the normal therapeutic dose [16,20,21]. A higher dose should be considered for UMs [21].

There is no discussion about the analytical validity (sensitivity and specificity of the genotype test) of CYP2D6 testing [22]. However, the clinical validity (ability of the test to predict the association of genotype with the circulating levels or clinical response predicted by the genotype), and clinical utility (likelihood that use of the test to guide drug choice will improve outcomes) of CYP2D6 testing to guide risperidone dosing are less obvious [23].

Many point at the potential benefits of personalized medicine in drug efficacy and tolerability [24], drawing on evidence demonstrating a relationship between the CYP2D6 genotype in a patient and the risk of adverse drug events and treatment failure due to such [16]. Trials have also demonstrated that the discontinuation of treatment with several antipsychotics leads to a lack of drug efficacy and intolerance [9]. Hence, a pharmacogenetic test used to stratify patients could enhance a higher rate of continuation on a pharmacotherapy while reducing the costs by improving the health outcomes derived from adverse drug events (ADEs) and the efficacy of the drug due to an improved drug management. However, as for any medical test, the clinical utility of pharmacogenetic testing for the use of risperidone in first episode schizophrenia patients needs to be tested. In situations where little evidence is available such as in this case, performing a health technology assessment (HTA) by means of modeling the potential economic and health benefits of pharmacogenetic testing in schizophrenia provides additional support for decision-making by both technology developers and decision makers [25]. An economic evaluation of the costs and health benefits derived from the use of a pharmacogenetic test in schizophrenic patients is currently lacking in the literature [26].

We conducted an economic evaluation to estimate the costs and health benefits of pharmacogenetic testing for the use of risperidone in first episode schizophrenia patients. The objective of this study was assess the potential cost-effectiveness of the use of CYP2D6 testing in treatment management for schizophrenia using a conceptual model that is valid and useful to this purpose given the limitations of data available.