

PHARMACOGENETIC TESTING IN PSYCHIATRY:  
PHARMACOECONOMIC APPLICATIONS AND CONSIDERATIONS

Renee Romeo, Katherine J. Aitchison, Delphine Capdevielle

Abstract

*Object:* To outline and discuss the pharmacoeconomic considerations of the application of pharmacogenetic testing in psychiatry.

*Method:* A search of literature relevant to the above was conducted, and, in addition, authors who have published in the field were contacted for their papers.

*Results:* Some psychopharmacological treatments will improve the everyday lives of patients; however, it is recognised that medications do not produce the same effect in everyone. Pharmacogenetic individualisation of treatment offers the potential of eliminating the cost of treating patients whose genetic composition renders them unlikely to respond to treatment or likely to suffer harm and of reducing the societal effects of untreated psychiatric disorders. Although there are costs associated with introducing pharmacogenetic testing, these should be weighed up against the potential benefits.

*Conclusions:* Economic evaluations are a useful tool to weigh up these costs and benefits associated with psychopharmacogenetic testing and not only offer evidence in respect of whether or not value for money is being provided, but may also be useful in supporting discussions or conflicts between stakeholders in developing and introducing pharmacotherapies employing pharmacogenetic testing.

**Key Words:** Pharmacoeconomics – Pharmacogenetics

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Context

Mental health problems in England are estimated to cost society more than £77 billion a year in care and support provided by the NHS, local authority, private sector, friends and family, hours of work lost, benefits paid due to illness and the human cost of reduction in quality of life and even mortality (Sainsbury Centre for Mental Health 2003). Employers are also affected by mental ill health in their workforce; it is estimated that the annual cost to employers of mental health problems among their staff is almost £26 billion (Sainsbury Centre for Mental Health 2007). The effects on employment

are more directly felt by families and the individual affected with mental illness, as it is not only a source of income but a source of social identity, self esteem and potentially social network expansion (Knapp 2003).

Some pharmacotherapies improve the everyday lives of patients; however, it is recognised that medications do not produce the same effect in everyone. The reasons for this may be due to genetic differences. It has been established that genetic differences point towards differences in the way polymorphic traits are distributed (Kirchheiner J et al. 2004, Bertilsson 1995, Wood 2001). There is also evidence that suggests that genetic make-up may influence the effective therapeutic

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response to psychopharmacological treatments (Arranz et al. 2000, Shaikh and Kerwin 2002).

Many drugs are only effective in 60% of people who take them. Some people may respond better to one medication than another, some may need larger dosages than others, some experience side effects, and others do not. Adverse drug reactions (ADRs) are the cause of death for 100,000 patients per year, making them the fifth leading cause of death in America (Herper 2001). It is estimated that the majority of the drug-related morbidity and mortality of \$136 billion (£68 billion) per year in the United States is related to adverse drug events (Nesbit et al. 2001, Johnson and Bootman 1995).

Tests that facilitate detection of genetic differences that affect drug response or result in adverse effects, commonly referred to as pharmacogenetic testing, have been proposed as potentially useful clinical tools for guiding treatment selection (Albers and Ozdemir 2004, Morley and Hall 2004). Two applications of pharmacogenetics are suggested by Morley and Hall (2004). Firstly, patients can be tested to determine the polymorphisms in their genes that may be used to predict treatment response prior to pharmacological treatment. An appropriate pharmacological treatment could then be selected that is likely to maximise therapeutic outcome. Secondly, it is recognised that pharmacogenetics could also aid drug development and provide a case for salvaging drugs which are not available for use because they result in side effects in a small group of people who cannot be identified before treatment. If pharmacogenetic testing can establish that for a subgroup of patients a drug is beneficial without producing side effects, the drug could in theory be marketed with the caveat that testing takes place prior to use to determine the risk of side effects.

### Costs associated with pharmacogenetic testing

Pharmacogenetic testing comes at a cost, and, the possibility of widespread use raises complex issues which could impact on many, including pharmaceutical companies, insurers, patients and health care providers.

The cost of genetic testing can range from under \$100 (£50) to more than \$2,000 (£1000), depending on the nature and complexity of the test. Costs are likely to increase if more than one test is necessary or if multiple family members must be tested to obtain a meaningful result. In countries with private health insurance, in many cases health insurance plans will cover the costs of genetic testing when it is recommended by a person's doctor. In countries such as the UK, where the use of genetic testing in psychiatry is in its formative stages, the impact for patients and health care providers both require consideration.

Under the National Health Service, psychiatric care is provided 'free at the point of use;' in this case costs are borne by health and social care providers, as well as by others, including carers. Testing patient populations with a relatively high prevalence of a mental disorder would be likely to lead to an increase in health care costs for the NHS. For many people with a mental illness, private psychiatric care supplements or even replaces existing statutory provisions where some forms of treatment are not available under the NHS. In this case

the cost of genetic testing may have to be covered by the patient requiring treatment, or their insurer.

Although there are costs associated with introducing pharmacogenetic testing, there may also be the potential for savings. In cases where associations between genetic polymorphisms and adverse drug effects are identified, certain drugs or drugs at an inappropriate dosage may not be administered to certain patients, thus preventing lengthy hospitalisations associated with serious adverse events from a given pharmacotherapy.

In a health care system with finite resources such as the NHS, clinical effectiveness on its own is insufficient to form a basis for introducing and identifying novel additions to pharmacotherapies, such as pharmacogenetic testing, for use in patients. This is largely because resources employed in introducing such testing could be used in other ways, for example to provide or expand treatments for psychiatry or physical health or in non-health areas such as education or national security. Novel additions have to demonstrate cost-effectiveness to be adopted by the UK National Institute for Clinical Excellence (NICE). Various relevant stakeholders including the government, the pharmaceutical industry, health care providers and organisations providing guidance on promoting good health therefore are considering the potential value for money of pharmacogenetic testing.

### Value for money in psychiatry

Pharmacoeconomic analyses in neuropsychiatry are not simply concerned with the economic impacts of drug treatment in psychiatric patients and their effects on the health care systems and society, but in addition compare the impacts - in terms of costs and outcome of one approach versus another. These impacts can be assessed in terms of the costs (of assays, medication, changes in health and non-health care services, changes in patient's time and carer's time for treatment and monetary impacts on the patient and care in terms of out-of-pocket payments) and outcome (in terms of quality of life, or therapeutic outcome).

The most commonly discussed pharmacoeconomic evaluations are cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). Other approaches include cost-minimization analysis (CMA) and cost-consequences analysis (CCA). These and other techniques all seek to weigh up improvements in outcome, per given budget or set of resources. They share common elements: in particular, they examine both 'interventions' such as medication, service use pattern, psychological treatment, and also costs and outcomes. They differ, however, in the analytical approaches including definition of the outcomes.

### Cost-minimisation analysis

Cost-minimisation analysis is not conventionally used by health economists as an approach to assess value for money, as the focus is only on costs. Typically, cost-minimisation analysis is used where the outcomes of the treatments are not significantly different. In practice,

CMA can only be justified where a prior view has been taken based on previous research or where the two treatments have a near identical chemical composition, for example drugs in the same pharmacological class.

### *Cost-consequences analysis*

In psychiatry, outcomes can be measured by the impact the treatment has on various aspects of physical and mental functioning. It may therefore be inappropriate to focus on only one measure of outcome. Cost-consequences analysis facilitates multiple comparisons: costs are presented alongside measures of relevant outcome dimensions for each intervention.

### *Cost-Benefit analysis*

Cost-benefit analysis assesses whether the consequences of a therapeutic intervention justify the costs. In this approach to assessing value for money, attempts are made to value the consequences of the intervention in monetary terms. If the monetary measure of outcome exceeds the cost, the intervention has a net benefit. With two or more alternatives, the intervention with the greatest net benefit would be suggested as providing best value for money. This type of evaluation allows policy makers to consider the merits not only of allocating resources within health care, but also to consider whether it would be more appropriate to invest in other sectors such as education. Cost-benefit analyses are thus intrinsically attractive to such decision makers; conducting them is, however, problematic because of the difficulties associated with valuing outcomes in monetary terms.

### *Cost-utility analysis*

Cost-utility analysis compares costs with a reduced measure of outcome in terms of changes in preference-weighted, health-related quality of life. Changes in quality of life are usually computed as a combined index of the length of life and quality of life such as the Quality Adjusted Life Year (QALY). CUA has an advantage over the other methods in that it is a generic measure which allows comparisons to be made across diagnostic or clinical groups (for example, comparing psychiatry with oncology or cardiology), and as a consequence is widely used in pharmacoeconomics. However, this measure is sometimes viewed as insufficiently sensitive to the kinds of change expected in treatments for mental health problems.

### *Cost-effectiveness analysis*

Another method widely used in pharmacoeconomics, largely because of its intuitive appeal, is cost-effectiveness analysis. This form of analysis measures outcomes using measures familiar from clinical studies and is employed to help decision makers choose between alternative interventions available to or aimed at specific patient groups. CEAs work with a single outcome

dimension - such as change in quality of life, the number of life years saved, the number of symptom-free days or the change in Hamilton Depression Rating Scale score - and then compute and compare the ratio of the difference in costs between the two treatments to the difference in outcome (the cost-effectiveness ratio, including the incremental cost-effectiveness ratio or ICER, see below).

Identifying costs relevant to pharmacoeconomic analyses is not always straightforward. Usually many agencies provide services to one individual, as the impact of both the illness and its treatment may be wide. The types and range of costs included in the analysis often depends on the viewpoint from which the analysis is being conducted. Not surprisingly, analyses can be taken from a number of viewpoints; there are as many points of view as there are stakeholders (namely the government, the pharmaceutical industry, health care providers, insurance companies, patients and carers) concerned with treatment for mental illness. The broadest and most comprehensive viewpoint is the societal perspective - which incorporates all costs, regardless of who incurs them.

Medications are often compared using any of the above approaches. Where two or more medications are being compared and there is clinical equivalence, the cheaper of the two treatments is preferred. However, decisions on introducing drug therapies are often not so straightforward. When new medications are introduced, they can be more expensive, but may have better outcomes. In such a case, an assessment of the additional costs associated with a unit increase in outcome is often made. This is often referred to as incremental cost-effectiveness ratios (the difference in costs between the old and the new treatment divided by the difference in outcome whilst being prescribed the old and new treatments).

The use of incremental cost effectiveness ratios by health care providers in making a decision regarding the introduction of a new drug is nevertheless not simple. Organisations that provide guidance on promoting good health through recommending drug treatments such as the National Institute for Clinical Excellence (NICE) in the UK are faced with an onerous task. Devlin and Parkin (2004) point to suggestions that decisions are made comparing the ICER with an absolute threshold of £30,000. However, Chidgey and colleagues (2007) dispute this, suggesting decisions are made 'on a case-by-case basis rather than using an absolute threshold,' after discussion with independent advisory committees and guidance groups, including consideration of issues such as equity and the relevant legal and policy constraints.

More recently, other techniques that move away from thresholds have been used to support decision making. Here the focus is on the value that needs to be placed on a unit of change in outcome for the new drug to provide better value for money relative to another.

### **Psychopharmacogenetic testing in pharmacoeconomics studies**

Data used to provide evidence on the costs and outcomes of drug treatment are usually available from a number of sources, the most popular being randomised

controlled trials (RCTs), naturalistic studies, and decision analytical models. The scope of this paper does not allow us to present in detail the 'pros' and 'cons' of each method. However, we summarise the approaches currently in use in psychopharmacoeconomic research, and discuss the approach that we believe would lend itself to predictive testing in psychopharmacogenetics.

In an RCT, the allocation to receive a new treatment is random and takes place in a controlled setting. It is widely muted as the 'gold standard' for evaluating treatment effects as randomisation avoids selection bias, which may lead to patients receiving the treatment having a systematically better or worse prognosis than controls, and facilitates standardisation of treatment.

Naturalistic studies, on the other hand, move away from the artificial conditions of the RCT, and observe cost and outcome related to treatment in routine clinical practice. Patients may in addition still be randomised to treatment in order to avoid selection bias. Despite continued widespread use of RCTs and naturalistic studies, the number of decision analytical models in pharmacoeconomics has grown over the years and is now widely used in evaluating drug treatment.

Decision analytical models are especially useful where the timing of events is important, and there is the risk of an event occurring. In choosing which treatment provides the best value for money, two types of models can be used: decision tree models, where the likelihood of an event occurring can be made by decision or chance, within a relatively short time frame; and Markov models for analyses with ongoing risk over a longer time frame. Data for these models can be obtained from clinical trials, naturalistic studies, and systematic reviews of the literature, or a combination of these sources.

Applied to genetic testing in pharmacogenetics, decision modelling is best used to assess costs in relation to outcomes, though other methods are possible. The advantage of using this approach is that the likelihood of possible events occurring as a consequence of adopting one pharmacotherapy over another is clearly mapped out. A simple decision model would require evidence on the relative response rate to treatment, effects of the drug treatment on health outcome such as impacts on quality of life and costs that may include costs of the medication, of the tests, and of health and social care (such as visits to a general practitioner, psychologist, community mental health team member, social worker, etc.), and/or may include costs of the impact on patients themselves (such as lost employment), carers and of the impact on the output of goods and services produced within society, the latter if assessed from a broader societal perspective.

There is likely to be uncertainty around monetary values given to such parameters and therefore sensitivity analyses can be used to assess the extent to which results may be influenced by changes to these values.

### Application of psychopharmacogenetic testing in pharmacoeconomics

The principles of this are outlined in Aitchison and Gill (2002). There is a growing body of evidence in regard to the clinical effectiveness of psychopharmacogenetics and the potential for genetic testing

to provide optimal care for patients where there are scarce resources. However, despite this widening evidence base, there is still a relative paucity of pharmacoeconomic studies in psychopharmacogenetics.

Perlis and colleagues (2005) performed a CEA of a genetic test that may identify individuals with a greater likelihood of responding to clozapine treatment. The authors found that applying the pharmacogenetic test and treating those predicted to respond to clozapine with clozapine cost \$47,705 (USD) (£23,852) per additional quality-adjusted life-year, compared with treating all patients with other antipsychotics and reserving clozapine for treatment-resistant patients.

The following illustration applies pharmacoeconomics to psychopharmacogenetics, and considers patients randomly assigned to one of two antidepressant treatments, a new drug and an existing treatment for depression currently on the market.

The new drug X is associated with a response rate of 40% and is more effective than drug Y with a response rate of 20%. The utility achieved from patients responding to drug X is 0.75 QALY compared with 0.25 QALY in those patients who do not respond and for drug Y the utility achieved for patients responding to treatment is 0.65 compared with 0.35 for those who do not respond (**Table 1**). However, the new drug (X) is more expensive than the old drug at £2,400 and £1,000 for drug Y. At a cost of £1,000 the QALY associated with drug Y is 0.41 ( $0.20 \times 0.65 + 0.8 \times 0.35$ ). In contrast, the cost of drug X is £2,400 and the associated QALY is 0.45 ( $0.40 \times 0.75 + 0.60 \times 0.25$ ). The gain in QALYs for the new drug X compared to the existing drug treatment Y is 0.04 at an additional cost of £1,400. Drug X therefore costs £35,000 ( $\text{£}1,400/0.04$ ) for each additional point improvement in QALYs (**Table 2**). Allowing for uncertainty or an error margin, if a third party payer is therefore willing to pay up to £30,000 for each additional QALY gain, then drug X would not be considered as the cost-effective option in comparison to drug Y.

Alongside these data, if genetic data were collected from blood tests, it would be possible to observe retrospectively whether a patient's genetic profile made a difference to the cost-effectiveness of the two drugs. Predictive testing can identify those patients, for whom there is a positive predictive value, *i.e.*, those patients who have a good response to treatment and test positive for the genetic variant, and of all patients who are tested and have a positive response.

Assuming the cost of the predictive test is £150, and the presence of a gene variant affects the response to drug X and drug Y in the above model, and that patients testing positive for the gene variant have a response rate for drug X at 60% and for drug Y at 50%, then the QALY gain of drug X compared to drug Y is 0.05 [ $(0.6 \times 0.75 + 0.4 \times 0.25) - (0.5 \times 0.65 + 0.5 \times 0.35)$ ], and the additional costs of drug X compared to drug Y at £1,400 remains the same, as all patients would be tested. Under predictive testing, drug X therefore costs £28,000 per additional point improvement in QALY. In this simple hypothetical example, the test identifies a proportion of the sample where the response rate among patients with the gene variant is slightly higher (60% versus 50%).

Dervieux and Bala (2006) provide a more advanced illustration and suggest that accurate estimates of costs

Table 1. Comparative outcome for drug X and drug Y without testing

Drug X			Drug Y		
Response rate	Utility (QALY)		Response rate	Utility (QALY)	
	Responders	Non-responders		Responders	Non-responders
40%	0.75	0.25	20%	0.65	0.35

Table 2. Comparison of alternative drug strategies for treatment without testing

Strategies	Comparison (Drug X-Drug Y)				
	Costs (£)	QALYs	Incremental costs (£)	QALY gain	Cost per QALY gain (£)
Drug X	2,400	0.45			
Drug Y	1,000	0.41	1,400	0.04	35,000

and clinical information is required to ensure that the results of any cost-effectiveness analysis are robust. Models are only tools to decision making, with their results depending on the inputs: assumptions in the parameter estimates and the data structure. It is therefore necessary that evaluators conduct modeling studies according to best applicable standards of quality (Weinstein et al. 2003).

### Wider economic feasibility considerations

The economic feasibility of rolling out psychopharmacogenetics will depend on the ability to resolve possible conflicts of interest. To date, pharmaceutical companies have not routinely incorporated recommendations for genetic testing into summaries of product characteristics (SPCs) for drugs that are subject to polymorphic metabolism. A notable recent exception to this is the SPC for aripiprazole (Electronic Medicines Compendium 2007), in which testing for CYP2D6 metaboliser status is mentioned.

The lack of routine incorporation of such information, where relevant, may be at least partly because the inclusion of pharmacogenetic testing may result in stratifying patients with a given clinical indication for the drug by genotype, which has implications for the number of patients for whom the drug would then be appropriate, and hence its "market share" in comparison to other drugs licensed for the same indication, and for the drug discovery pipeline (companies may need to consider developing different drugs for each phenotypic group, which may be seen as uneconomic, Horrobin 2001). Producing drugs for patients with rare genotypes could therefore be viewed as unviable and lead to patient

groups for whom there are no available therapeutic treatments. The decision not to produce therapies for relatively small patient groups may be at odds with societal or political preferences and decision makers will need to ask themselves whether it is ethical to not treat some patients because they have a rare genotype. In light of this, there needs to be some consideration of whether special concessions should be given to drug companies to develop treatments for minority patient groups and discussion of whether or not there are differences in the value of the health gain to individuals with a common disorder versus those with a rare disorder (McCabe et al. 2005), factoring in the severity and impact of the disorders.

There may, conversely, also be treatments with no known suitable patient groups, known as orphan therapies (Danzon and Towse 2002). In the case of the latter, it is possible that pharmacogenetic testing could identify patient groups for which these therapies would in fact be appropriate, thus making these drugs clinically available with a relative low additional drug development cost.

There also remains the practical issue of the feasibility of introducing pharmacogenetic testing for those with mental illness who may be reticent towards it. While there are conflicts to resolve between various stakeholders, it seems fair to assume there are potential benefits from pharmacogenetic testing in psychopharmacotherapy. However, to date there is little empirical evidence to guide decision making of whether this will provide value for money. Economic evaluations are a useful and necessary tool in offering and assessing evidence, which may not only assist in resolving resource allocation issues, but support discussion between the relevant stakeholders.

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