Testing for cytochrome P450 polymorphisms in patients with schizophrenia on antipsychotics

Executive summary

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Objectives

The overarching questions that this review aimed to answer were:

- Could testing for cytochrome P450 (CYP) polymorphisms in adults entering antipsychotic treatment for schizophrenia lead to improvement in outcomes?
- Are testing results for CYP polymorphisms useful in medical, personal or public health decision-making?
- Is testing for CYP polymorphisms in schizophrenia patients treated with antipsychotics a cost-effective use of health-care resources?

Background

Mental health is recognised as a major challenge in UK clinical practice and as such it is one of the nine National Service Frameworks. Schizophrenia is a condition requiring immediate attention but it is complex both to diagnose and to treat. Treatment of schizophrenia is especially difficult because of the large amount of interindividual variability in patient response to therapy. This high degree of heterogeneity is associated with adverse drug reactions (ADRs) or therapeutic failure, which has important implications for both the patient and the UK NHS.

The interindividual variability to therapy may in part be explained by differences in the enzymes responsible for metabolising drugs to their excretable forms, in particular the CYP enzyme system. A number of antipsychotics (both typical and atypical) are metabolised by CYP2D6 and CYP3A4, and to a lesser extent CYP1A2, including haloperidol, risperidone and clozapine.

Diagnostic genotyping tests for certain CYP enzymes are now available. The first licensed test is the AmpliChip® CYP450 test, which tests for both CYP2D6 and CYP2C19. CYP testing for prescribing antipsychotics to schizophrenia patients would be attractive if it could improve response rates or reduce side effects from treatment.

Methods

A systematic review of the analytical validity, clinical validity and clinical utility of CYP testing was undertaken. A review of economic evaluations of CYP testing in the field of psychiatry was also undertaken, as was a review of schizophrenia models.

Several search strategies were used in various databases including EMBASE, MEDLINE and the Cochrane Library. Searches related to analytical and clinical validity were carried out up to January 2008, whereas searches for clinical utility were carried out up to March 2008.

Data were extracted into structured tables and are narratively discussed in the relevant sections of the report. Meta-analysis was also undertaken where possible. For the purpose of meta-analysis, patients with multiple copies (more than two) of wt alleles were considered to be wt/wt, which it should be noted may dilute effects, given that such patients are ultrarapid metabolisers (UMs) and so will metabolise drugs quicker than patients with just two wt alleles. Given data limitations, economic modelling was not feasible, therefore key issues relating to the existing evidence base and future research needs were narratively discussed.

Inclusion criteria

For the reviews of analytical validity, clinical validity and clinical utility any study design except single case studies was included. In the case of analytical validity any patient population was accepted, whereas in the case of clinical validity and clinical utility only adults with schizophrenia receiving treatment were included. Outcome measures included accuracy of the test, measures of pharmacokinetic bioavailability, efficacy, ADRs and clinical outcomes.

For the economic literature review, economic evaluations that considered both the costs and the benefits of CYP testing were included in the review. For the review of schizophrenia models, models were included if they modelled antipsychotic
therapy in any schizophrenia population and if they were published in English.

Results

Clinical evaluation

For analytical validity, 46 studies of a range of different genotyping tests for 11 different CYP polymorphisms (most commonly CYP2D6) were included. Sensitivity and specificity was typically found to be 99–100%. For clinical validity, 51 studies were found in which very few patients had either the mut/mut genotype or multiple copies (more than two) of the wt allele. These studies mainly focused on ADRs; there was some evidence from prospective studies of patients tested for CYP2D6 that, compared with those with the wt/wt genotype, patients with the wt/mut and mut/mut + wt/mut genotypes were at increased risk of tardive dyskinesia (TD) [odds ratio (OR) 2.08, 95% confidence interval (CI) 1.21 to 3.57, and OR 1.83, 95% CI 1.09 to 3.08 respectively]. In cross-sectional studies, those with the mut/mut genotype also had higher Abnormal Involuntary Movement Scale (AIMS) scores (measuring TD severity) than those with the wt/wt genotype [weighted mean difference (WMD) 1.80, 95% CI 0.40 to 3.19]. The only other significant finding was that patients with the CYP2D6 mut/mut + wt/mut genotype were significantly more likely to develop parkinsonism than those with the wt/wt genotype (OR 1.64, 95% CI 1.04 to 2.58). No published studies were found that met the inclusion criteria for clinical utility.

Economic evaluation

Only one economic evaluation assessing the costs and benefits of CYP testing for prescribing antidepressants was identified from our search and subsequently included in our review. Although not directly relevant to our decision problem the study did highlight the difficulties in undertaking an economic analysis in this area. Results from our search for a suitable schizophrenia model for adaptation and use in our review identified a total of 28 models, none of which was suitable for our purposes.

The absence of published economic studies of CYP testing for schizophrenia, the lack of evidence from the clinical component of this review and the unsuitability of published schizophrenia models meant that no model was developed; instead, the key features and data requirements of an economic model were discussed. This identified that there are still a number of factors that are unknown both for schizophrenia as a condition and in relation to the CYP pharmacogenetic test.

Conclusions

From this review of the literature, tests for determining genotypes appear to be highly accurate. However, not all aspects of analytical validity have been reported in the studies (quality control and assay robustness being commonly neglected). In terms of clinical validity, research is being conducted to assess the links between genotype and metabolism and ADRs. However, to date the research is limited and no firm conclusions can be drawn. No studies assessing clinical utility have been reported.

In terms of assessing the cost-effectiveness of using such pharmacogenetic testing, in the opinion of the authors it is too soon to tell. An economic model was not developed as a part of this report but, from previous work carried out in the area of pharmacogenetic testing in depression and through the assessment of published economic models of schizophrenia, a suggested model framework has been developed.

Our proposed model framework consists of four main modules: pharmacogenetic test module (assigning patient to phenotype), clinical effects module (linking phenotype to outcomes), transitional module (effect of test results on clinical decision) and the schizophrenia module (projecting treatment effects over a patient’s lifetime). Without all four components and the information to populate them it is not possible to determine the cost-effectiveness of CYP testing in schizophrenia.

However, on the basis of a single test per patient costing around £300, the expected lifetime benefit per patient need be only about 0.01 quality-adjusted life-years (QALYs) to achieve cost-effectiveness of ≤ £30,000 per QALY gained. If any survival improvement can be shown to be supported by evidence then this level of gain appears to be modest, particularly if opportunities arise to target testing to those patients most likely to show improvements in their care and expected outcomes. Therefore, CYP pharmacogenetic testing still shows promise, but further research is needed.
Recommendations for future research

Although the current evidence base does not support the use of pharmacogenetic testing in this area, it does indicate that further study in each of the key areas is needed to either demonstrate or refute the ability of pharmacogenetic testing to assist in the development of individualised patient care in the area of schizophrenia. Recommendations for future research cover both aspects of research quality and data that will be required to inform the development of future economic models.

Analytical validity

- Studies of analytical validity need to be explicit about patient selection, quality control, assay robustness and the sensitivity and specificity of tests. Study findings should not only report on allele frequencies but also report appropriate genotype data.

Clinical validity

- Further evidence is required to link phenotype to genotype. Such studies need to include larger numbers of patients with the UM (multiple copies of the wt allele) and poor metaboliser (mut/mut) phenotypes and be prospective in design.
- Studies need to consider the impact of environmental factors such as smoking, concomitant medicines, medication adherence and ethnicity. In relation to medication adherence, genotypes need to be related not only to clinical parameters but also to pharmacokinetic parameters.
- Studies need to ensure that all currently used antipsychotics are investigated. However, given the uncertainty about the full extent of the role played by CYP2D6, further studies focusing on patients taking risperidone and olanzapine would also be useful.
- Future research will need to consider a comprehensive approach that considers not only CYP isoforms involved in the metabolism of antipsychotics but also other targets such as dopamine and 5-hydroxytryptamine receptors.

Clinical utility

- Prospective clinical utility studies are needed. As with clinical validity they should ensure that all currently used antipsychotics are investigated although, given their importance to the NHS (and the uncertainty about the full extent of the role played by CYP2D6), further studies focusing on patients taking risperidone and olanzapine would be particularly useful.

Economic evaluation

- Improved evidence should be sought on the link between improved schizophrenia care and life expectancy.
- Collection of longitudinal data that identify patterns of adherence, length of time in relapse and cost of care (including care provided in the community) is required.
- A common approach to the measurement and reporting of adherence, relapse and quality of life in schizophrenia is needed.

Publication

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