The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation


CRD summary
This review concluded that tests for determining the genotypes for cytochrome P450 polymorphisms appeared to be highly accurate, but were not always well reported. There was limited research on the clinical validity of these tests for adults entering antipsychotic treatment for schizophrenia and no firm conclusions were possible. There were no completed studies on their clinical utility. These conclusions are likely to be reliable.

Authors' objectives
To determine the clinical effectiveness and cost-effectiveness of testing for cytochrome P450 (CYP) polymorphisms, in adults starting antipsychotic treatment for schizophrenia, to aid the making of medical, personal, or public health decisions.

Searching
The Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, DARE, EMBASE, HTA, Web of Knowledge, MEDLINE, and PsycINFO databases were searched for articles from 1995 to March 2008. The full search strategies were reported. Internet searches and consultations with experts and members of the advisory panel were also undertaken. Only studies reported in English were eligible for inclusion.

Study selection
Analytic validity studies of any design, except single-case studies, were included if they were of individuals genotyped for any CYP polymorphism and reported the accuracy of the test. Clinical validity studies of any design, except single-case studies, were included if they were of adults with schizophrenia, who were receiving treatment with antipsychotics and were genotyped for CYP polymorphisms. These studies had to report pharmacokinetic outcomes, efficacy outcomes, or outcomes relating to adverse drug reactions. Clinical utility studies of any design were included if they enrolled adults who were treated with antipsychotics and were genotyped for CYP polymorphisms. These studies had to report the results of the prospective prediction of clinical outcomes; the modification of clinical management; the use in medical, personal, and public health decision-making; or the harms, associated with CYP genotyping.

Most of the analytical validity studies were conducted in Europe. The most commonly used methods were real-time polymerase chain reaction (PCR), microarrays, multiplex methods, and pyrosequencing. The most commonly examined polymorphism, tested in almost half of the studies, was CYP2D6. Limited information was available to the authors on the ethnicity of participants. Most of the clinical validity studies also assessed the impact of alleles of CYP2D6. A range of different antipsychotics or combinations of antipsychotics were taken by patients in the clinical validity studies; a minority of these studies were restricted to patients taking typical antipsychotics. The most commonly assessed outcome was adverse drug reactions.

Two reviewers independently assessed studies for inclusion, using a validated standardised form.

Assessment of study quality
There was no formal assessment of analytic validity studies, but general issues relevant to genetic association studies were assessed. Clinical validity studies were assessed using the criteria recommended by the Centre for Reviews and Dissemination (CRD) and a tool specific to pharmacogenetic studies. Clinical utility studies were not assessed for validity due to the limited data used. The authors did not report how many reviewers assessed validity.

Data extraction
Data to permit the calculation of odds ratios for dichotomous outcomes and mean differences for continuous outcomes, both with 95% confidence intervals, were extracted into structured tables by one reviewer and checked by a second
Methods of synthesis
Where possible, studies were combined using fixed-effect meta-analysis to calculate the pooled odds ratio or weighted mean difference, with 95% confidence interval. Heterogeneity was assessed using the $I^2$ statistic and visual inspection of forest plots. A random-effects analysis was planned where significant heterogeneity was detected.

Where statistical pooling was not possible, a narrative synthesis was presented, with studies grouped by their nature and the alleles investigated.

Results of the review

Analytic validity: There were 46 studies of 11 single nucleotide polymorphisms and sample sizes varied from 40 to 428 individuals, with the number of samples assessed ranging from six to 1,400. Tests for determining genotypes were highly accurate, with a concordance of 100%. Where specificity and sensitivity, or the data to allow the calculation of these, were reported they were both between 99% and 100%, with one exception. Detailed results for each CYP genotype were reported. Frequently, some aspects of analytic validity were not reported, particularly quality control and the reliability of the process.

Clinical validity: There were 47 studies and the sample sizes ranged from nine to 309 patients, with a mean of 101 and a median of 92; the authors considered these to be small samples for studies of this type. There was limited reporting of some aspects of study validity. A wide range of outcomes, including a large number of adverse drug reactions were investigated. The only significant outcomes were for CYP2D6 (37 studies), where: patients with the wt/mut and mut/mut genotypes were at increased risk of tardive dyskinesia compared with those with the wt/wt genotype; the abnormal involuntary movement scale scores were more favourable for patients with the wt/wt genotype; and this group was significantly less likely to develop parkinsonism than those with other genotypes. The majority of these patients were taking typical antipsychotics.

Clinical utility: There was one ongoing randomised controlled trial and one observational study. No data were available for the trial. Limited data from the observational study (93 patients) produced inconclusive and contradictory findings and the authors recommended extreme caution in interpreting the results.

Cost information
It was not possible to develop an economic model for the use of CYP genotyping, instead, the key features and data requirements of such a model were discussed and a framework was suggested. This framework indicated that, with a single test costing £300, cost-effectiveness, at a threshold of £30,000 per quality-adjusted life-year (QALY), would be achieved with a lifetime benefit per patient of 0.01 QALYs.

Authors' conclusions
Tests for determining genotypes appeared to be highly accurate, but some aspects of analytic validity were not generally reported. Research on clinical validity was limited and no firm conclusions could be drawn. There were no reliable studies on the clinical utility of these tests.

CRD commentary
The review questions were clear and they were supported by clear, but relatively broad, inclusion criteria. The authors searched multiple relevant databases and other sources, and steps were taken to minimise publication bias. Studies were limited to those reported in English, which might have led to the omission of relevant studies and the introduction of language bias. The authors reported using measures that were designed to reduce reviewer bias and error in the selection of studies and the extraction of data; it was not clear whether these measures were used in the assessment of validity. The validity assessment used appropriate criteria, where possible. The approach to synthesis was reasonable.

The authors' conclusions reflect the limited nature of the evidence and are likely to be reliable.
Implications of the review for practice and research

Practice: The authors did not state any recommendations for practice.

Research: The authors made a number of recommendations for research. They stated that analytic validity studies should be specific about patient selection, quality control, assay robustness, and the sensitivity and specificity of tests. They should report appropriate genotype data in addition to allele frequencies. Clinical validity studies should link phenotype to genotype and they should be prospective and include larger numbers of patients with ultrarapid metaboliser (multiple wt allele copies) and poor metaboliser (mut/mut) phenotypes. The impact of environmental factors should be related to clinical and pharmacokinetic parameters. Studies should investigate all prescribed antipsychotics, particularly risperidone and olanzapine. Targets other than CYP isoforms should be investigated, including dopamine and serotonin (5HT). Studies of clinical utility that investigate all prescribed antipsychotics, particularly risperidone and olanzapine, were required. There was a need for improved evidence on the link between schizophrenia care and life expectancy, with longitudinal data on the patterns of treatment adherence, relapse durations, and costs of care, and a common approach to the measurement of these parameters.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.