Sundhedsstyrelsen
Danish Health and Medicines Authority

RUTINE USE OF CYP-TEST IN ANTIPSYCHOTIC DRUG TREATMENT

– a health technology assessment
Summary

2012

Health Technology Assessment – funded projects 2012; 12(4)

Rutine Use of CYP-test in Antipsychotic Drug Treatment – a health technology assessment; Summary

URL: http://www.dacehta.dk

Key words: technology, patient, organisation, economy, health services research, health technology assessment, HTA, individualized medicine, Cytochrome P450, CYP2D6, CYP2C19, skizophrenia, anti-psycotics, genetest, individualised drug treatment psychiatry, dosis individualism, genetic testing, genotyping

Language: English summary of the full report in Danish

Format: pdf
Version: 1.0
Version date: October 25 2012

Issued by: National Board of Health, Denmark, November 2012

Design of report template: National Board of Health and 1508 A/S
Layout of the report: Rosendahls-Schultz Grafisk A/S
Design and layout of front page: Wright Grafics

Electronic ISSN: 1601-586X

This report should be cited as follows:
Jürgens G, Herbild L, Jacobsen C, Andersen SE, Rasmussen HB, Werge T, Nordentoft M, Jensen H
Rutine Use of CYP-test in Antipsychotic Drug Treatment – a health techonology assessment; Summary
Copenhagen: The Danish Health and Medicines Authority, Danish Centre of Health Technology Assessment (DACEHTA), 2012
Health Technology Assessment – funded projects 2012; 12(4)

Series title: Health Technology Assessment – funded projects
Series editorial board: Diana Reerman & Line Holt

For further information please contact:
The Danish Health and Medicines Authority
Danish Centre of Health Technology Assessment (DACEHTA)
Axel Heides Gade 1
DK-2300 Copenhagen
Denmark

Phone: +45 72 22 74 00
E-mail: dacehta@sst.dk
Home page: www.dacehta.dk

The English summary can be downloaded at www.dacehta.dk

What is Health Technology Assessment?

Health Technology Assessment (HTA) contributes to decision making in the health care sector. A HTA collects and assess existing knowledge about a given health technology. A health technology is defined broadly as procedures and methods for prevention, diagnostics, treatment, care and rehabilitation including devices and medicine. An example could be a new method to treat patients. Focus is on healthcare, patient, organisational and economical aspects. New research can be conducted if the number of sufficient studies is limited to elucidate one or more of these aspects.

The HTA results in a report that can contribute to better planning, quality enhancement and prioritizing in the health care sector. The target group is decision-makers in the health political field. The primary users are therefore administrations and politicians and other decision-makers in the health political field. The HTA contributes to decisions within administration as well as political management as to which services should be offered in the health care sector and how they should be organized.

Health technology assessment is defined as:

- HTA is a comprehensive systematic assessment of the prerequisites and consequences of applying a health technology
- HTA is a research-based, application-oriented assessment of relevant existing knowledge about problem areas applying a technology within the field of health and illness.

The project is funded by a HTA-fund that was terminated in 2007. The purpose of the fund was to spread out knowledge and use of HTA locally. The funded HTA-reports are prepared in collaboration with an external interdisciplinary project group. The project group systematically reviews the existing literature, contributes with data collection and produces the chapters and conclusions of the report. The project management is placed at the National Board of Health who is also responsible for the editing of the final report. The report has been submitted to an external reference group and is also externally peer-reviewed.

Find more information about HTA at www.sst.dk/mtv under HTA toolbox:
“Handbook of Methods for Health Technology Assessment”
“Health Technology Assessment – Why? What? When? How?”

Summary

Introduction

A large part of the psychotropic drugs that are currently used in psychiatry, are metabolized by the enzymes Cytochrome P450 2D6 (CYP2D6) and Cytochrome P450 2C19 (CYP2C19). Both enzymes exhibit genetic polymorphism. This means that there are variations in the genes encoding the enzymes that cause changes in the enzyme's metabolic activity. Thus, 5-10 % of the Caucasian population have a CYP2D6-genotype resulting in a significantly reduced enzyme activity (poor metabolizers (PM)) while 30-40 % have a slightly reduced enzyme activity (inter-media metabolizers (IM)) compared with the normal population (extensive metabolizers (EM). Approximately 1 % has a significant increase in the metabolic rate (ultrarapid metabolizers (UM)). For CYP 2C19, 2-3 % of the population are PM's, while the frequency of occurrence of UM's is unknown.

The genotype of both CYP2C19, CYP2D6 is analyzed by means of a simple blood test, also called CYP-test. It is used to predict an individual's ability to excrete drugs metabolized by the enzymes CYP2D6 and CYP2C19.

It is well documented that PM's achieves significantly higher drug concentrations at a given drug dose, while the concentrations in UM's is correspondingly low. PMs are generally considered to have an increased risk of adverse drug reactions, while UM's risk treatment failure due to relative under dosing. In theory, individualization according to the CYP-test results could improve these conditions. This, however, has never proven scientifically. In addition, ethical, organizational and social aspects of genotyping are largely unknown, despite the fact that these aspects are likely to be significant for the use of gene tests in clinical practice.

Despite this, the CYP-test is widely used in psychiatry. In 2006, a regional board of mental health care specialists (H:S Sundhedsfagligt Råd for Psykiatri) released recommendations to implement genotyping in treatment routines, and several centers have established the necessary laboratory facilities.

In the present MTV, we have chosen to focus on antipsychotic drug treatment, although the principles of the genetically determined drug metabolism also apply to other therapeutic areas – somatic and psychiatric. The reasons are mainly practical, as patients with diagnoses in the schizophrenic spectrum – who are the primary target for antipsychotic drugs – are a large part of the psychiatric patient population. Numerous antipsychotic drugs are metabolized by CYP2D6, which metabolic activity far more often is affected by genetically changes than CYP2C19. In other words, there are more PM's for CYP2D6 than CYP2C19. Finally, antipsychotic drug treatment is complicated by the frequent occurrence of side effects and treatment failure, which can lead to poor treatment adherence and increased risk of recurrence of illness and readmissions.

Purpose

In this HTA we want to answer the question whether CYP-test should be used as a routine measurement in psychiatry with focus on antipsychotic drug treatment considering its effect (technology), organizational aspects, the patient's perspective and cost-effectiveness (economy).

Target group

The primary audience for this report is the leading consultants in psychiatric wards, who will take the decision to introduce CYP-test as a routine measure, but other decision makers at departmental, hospital and regional level may also find the report useful.

Delimitation

The present HTA evaluates only the routine use of genotyping for CYP2D6 and CYP2C19 (CYP-test) in connection with antipsychotic drug treatment in psychiatry. The use of the CYP-test for a particular indication or testing of the genes coding for the other CYP-enzymes, which may also be involved in the metabolism of psychiatric drugs (including antipsychotics), is not mentioned. Although many patients with psychiatric disorders also receive drugs for somatic disorders such as diabetes, asthma or hypertension, the use of CYP-test for medical treatment of somatic disorders is not within the scope of this report.

Method

The main study in this project is a randomized, controlled trial of the clinical efficacy of routine use of the CYP-test. In order to use existing data available at the largest Psychiatric Centre in Denmark, Psychiatric Center Sct. Hans, two retrospective cohort studies based on medical records were conducted. The aim was to analyze whether the individual patient's CYP2D6 and CYP2C19 drug metabolizing capacity, is reflected in the psychiatrists prescription pattern of antipsychotics as well as adverse medication (anticholinergic drugs).

A third retrospective cohort study combines a quantitative and qualitative approach using descriptive data from medical records and ethnographic observations to elucidate whether CYP-test result affects the choice of treatment. In addition, an ethnographic field study of CYP-test's ethical, patient-related and organizational consequences and an economic study of cost implications and cost-effectiveness of the use of CYP-test were conducted.

Furthermore, a systematic literature review of the HTS's different subject areas (clinical, economic, and social science) was performed.

Technology

The CYP-test is a genetic test. By means of a single blood sample genes encoding the drug metabolizing enzymes CYP2D6 and CYP2C19 are analyzed. The genotype used to predict individual patient's ability to excrete drugs metabolized by these enzymes. The intention is to individualize drug treatment according to the patient's genetic profile and thereby reduce the risk of side effects or treatment failure.

In order to utilize the CYP-tests information effectively, a number of preconditions must be fulfilled. Firstly, the CYP-genotype must be associated with a relevant clinical outcome, such as increased risk of adverse reactions or therapeutic failure. Next, the CYP-test result must be translated into a medical decision, which ultimately should lead to an improved treatment. The technology section attempts to elucidate these aspects by answering the following HTA-questions:

- Are CYP2D6 and/or CYP2C19 genotype associated with an increased risk of adverse events or treatment failure associated with antipsychotic drug treatment?
- Does the CYP-test in its present state affect the choice of antipsychotic drug and dosage in patients with diagnosis within the schizophrenic spectrum?
- Does the systematic use of the CYP-test lead to improved treatment persistence with antipsychotic drugs, fewer side effects and better treatment effect?

There is evidence that poor (PM) and intermediate metabolizer (IM) status of CYP2D6 is associated with an increased incidence of antipsychotic drug induced side effects. However, we have no scientific evidence that this is also the case for CYP2C19. From a theoretical point of view, however, we expect that this is the case. But even though the association between CYP genotype and adverse drug reactions is essential for a meaningful use of CYP-test in daily clinical routines, it does not necessarily mean that the CYP-test result can be used prospectively as a decision making tool to improve the clinical outcome of antipsychotic drug treatment. It has not been possible to find an answer to this important question in the literature. The same is true for the question whether or not the CYP-test result is used in the complex process of medical decision-making. Therefore, the researchers behind the technology section of this report conducted four studies – three retrospective, descriptive studies and a randomized, controlled trial. Based on these studies, we realized that the CYP-test in its present state only rarely is used for the choice of drug and dosage and is only rarely part of those consideration of the patient's drug therapy that are documented in the patient files. We also showed that routine use of CYP-test as a tool to facilitate decisions regarding antipsychotic drug treatment does not improve treatment persistence, lead to fewer side effects, better treatment effect or better compliance.

Organization

The review of the existing, although sparse, literature and a case study conducted at one selected department, points out a number of organizational barriers to a meaningful utilization of the CYP-test in daily clinical practice.

This HTA answers the question: How does the organization contribute to a meaningful utilization of the CYP-test in daily clinical practice? Focusing on the fact that the CYP-test is used, when clinically meaningful, the analysis is guided by the following sub-questions:

- Do physicians' experience that the test is clinically meaningful?
- Is the CYP-test meaningful in workflows?
- Is the CYP-test meaningful in everyday clinical activities?
- Is the CYP-test meaningful in everyday relationships, interaction and the sharing of knowledge?

The overall conclusion is that the CYP-test tends to be absent in daily clinical practice due to organizational barriers – even where it in principle is part of the clinical routine.

Physicians are unsure whether the test is clinically meaningful: Both existing research and the empirical results from this study show that the majority of physicians do not have a clear position on whether CYP-test is clinically meaningful. Some hesitate. Some see benefit in some cases, but may at the same time have a lot of experience with situations where the test did not contribute meaningfully to the clinical work.

A place in the workflow: In line with what is found in a New Zealand study, we found that the test results come too late into the medical decision-making process. One reason is the time it actually takes from the blood sample is ordered until the test result is analyzed. An equally important reason is that test results easily disappear out of doctors' awareness due to workflow and available filing systems. A meaningful use of the CYP-test requires work to ensure the CYP-test a place in workflows and filing systems, which makes the test visible at the right time for the right practitioners.

The CYP-test in everyday clinical activities: In everyday clinical activities, the CYP-test is just a tool among many others in the medical decision-making. A tool is used in the same way and in the same situations as the other. In practice, the CYP-test is perceived and used as a blood test very similar to drug concentration measurements. Used like this the CYP-test often appears less relevant than other clinical tools. It only gives information for a minority of patients (in contrast to many other tools which provide relevant results for all), and might not be relevant in the situation where the results becomes available (e.g. because the patient at the time is not treated with CYP2D6-dependent medication). Typically, the physicians who participated in this study did not consider the CYP-test as a test of relevance far into the future.

CYP-test in everyday relationships, interaction and knowledge sharing: The international literature has pointed out that physicians' level of knowledge is too low. This study, however, points out something else, namely: that the knowledge required to use the test in clinical routines is relatively simple, but physicians must acquire it individually. This creates inconsistency in the way the test is used and test results are interpreted. In addition, it is a barrier to mutual knowledge exchange, which could help to make the test relevant, meaningful and present for physicians.

Research on implementation has highlighted that it is crucial to a new technology to be part of the peers' active discussions. However, at the center where this study took place, the CYP-test only rarely was subject of discussion and knowledge exchange. This was in part because physicians felt that the CYP-test result was not relevant in interdisciplinary fora, but also because the focus of these fora was on rehabilitation and 'creation of good lives' not details in medical adjustment. Overall, the CYP-test only rarely found a meaningful role in everyday relationships, interaction and knowledge sharing. An exception is a conference on polypharmacology, in which physicians in one of the studied departments participated – that is, a special forum where physicians discuss adjustment of medical treatment.

Overall, this study demonstrates that effective use of CYP-test requires extensive work with the organizational issues concerning the CYP-test that can ensure fora for active knowledge sharing and a collective awareness of its use and relevance (and irrelevance). Workflows and filing systems must be adapted to ensure that CYP-test answers are visible and easily accessible to the right person at the right time. Finally, the understanding of CYP-test as a blood test like any other must be addressed in order to ensure its optimal use.

The Patient

Patients in focus in this HTA receive psychiatric treatment of diseases of a chronic nature. Their treatment is often characterized by long-standing relationship with (different) physicians and by cooperation with the psychiatrist about continuous adjustment of their medical treatment. Based on this, this HTA has interviewed patients

about their experience with medical decision-making and the CYP-test. We have mirrored their experience with the experience of the psychiatrists and their practice within a selected ward. On this background, the HTA answers the following questions:

- What ethical issues should be considered in the routine use of genotypic testing?
- What factors affect whether patients will experience genotyping as an advantage or not?
- What role does genotyping play in the patient's participation in medical decision-making?

Today, CYP-testing is considered ethically unproblematic – a blood test that does not require special informed consent.

The potential of the CYP-test lies within the knowledge, which the patient can use for the rest of his/her life. It requires that the patient gets profound information about their CYP-status and its consequences. However, it is rarely practiced among the interviewees in this study. As to the psychiatrists in this study, key of the CYP-test is not its lifelong potential relevance, but rather the help it provides in the clinic in situations where it is difficult to find the right medication. For them it is a blood test similar to other blood tests. They do not consider it as a genetic testing, and they do not inform the patients about this fact, unless the patients specifically ask. And practically, they never do.

It should be considered, if such practice is appropriate. Literature on the topic considers it unlikely that this type of test would have any major impact for patients in the short term. However, recent research also points out that the test might prove to contain secondary information. Based on this, thorough information and confidential data keeping become important.

All things considered, this study points out an ethical need of:

- supporting the psychiatrists' use of informed consent and information about blood tests in general, and the CYP-test in particular
- supporting psychiatrists' focus on what the test means to the patient (i.e. knowledge that can follow them for the rest of their lives), rather than what it means to the psychiatrists here and now (i.e. knowledge that can support a medical decision in the current situation)
- supporting the fact that relevant knowledge about the test is given to the patients in a way, so that they understand it.

By giving good information to the patient concerning the CYP-test and effective dissemination to future therapists, one can ensure that CYP-test can be included in many decisions about change of medication, which psychiatric patients will encounter during their lives.

The way in which the CYP-test is included in the co-decision about medication is crucial for the extent to which the patient will experience its benefit.

The interviewed psychiatrists and patients in this study are of one mind when it comes to the value of a shared medical decision-making.

Both psychiatrists and patients emphasize the importance of making the patient's experience of effect and side effects crucial elements in any decision on medication – regardless of the CYP-test result.

For the patients, it is crucial that the psychiatrist listens, that two parties have assessed whether the medicine helps or not, that they have been involved in the decision, that they can attach a hope for improvement to the treatment – and that they do not experience too many side effects.

These factors must be considered in order for the patients to experience CYP-test as an advantage.

Many patients (and everyone in this study) have bad experience with over-medication or medication leading to many side effects. From a patient's perspective, a technology that can decrease the medication (and/or medication errors) is welcome – if it works as intended and is used in line with the above conditions.

Health Economics

The primary purpose of the health economic analysis is to compare the cost of the current treatment practices with a routine use of CYP-test. Thus, this HTA answers the question: Will the routine use of CYP-test lead to a more cost-effective use of resources compared with current clinical practice without the use of CYP-test?

The results from the clinical randomized study suggest modest effects of the intervention. The economic analysis is carried out as a separate analysis of the costs (cost minimization). The purpose is to check whether there is a lower cost of treatment on the basis of CYP-test, compared with current clinical practice.

The health economic analysis is based on data on consumption of health services among the patients included in the clinical randomized trials. Costs among patients in the intervention group compared with the costs among patients in the control group.

The health economic analysis suggests that routine use of CYP-test is cost neutral, even with a tendency to induce savings in the region of 23-24 % of the total treatment costs in health care within a year. During the 365 days which costs are summed over, there was an excess consumption of psychiatric treatment equivalent to 239 % in patients belonging to the group of extreme metabolizers. This excess consumption was reduced by 29 % among patients treated on the basis of CYP-test. Both results are highly statistically significant. This large and highly significant difference in cost could not be found when looking at the effects of intervention despite drug gateway status. This is due to the wide dispersion in cost, and that the extreme drug metabolizers constitute "only" 20 % of the total patient basis.

The lack of statistically significant difference in the total cost of the intervention and the control group does not mean that the difference does not exist. It has however not been possible to show with the sample size of this study. The result is hardly irrelevant from a priority setting perspective since the analysis shows that the use of CYP-test at worst is cost neutral and can reduce the cost of treating cumbersome schizophrenic patients by 29 %.

As expected, the analysis also showed that the probability of resource utilization in primary care is affected by whether the patient has an extreme drug reaction or not. Unfortunately, it has not been possible to estimate how this probability is affected by the intervention, as there was only one extreme drug turnover without consumption in the intervention group.

The costs of pharmacy-dispensed drugs are also found to depend on drug metabolism. Thus, the results show that the extreme metabolizers incur only half as high expenses for pharmacy dispensed medicine as normal metabolizers. However, patients in the intervention group incur costs, between 175 to 260 % of the equivalent in the control group. Note that drug consumption, as it is stated here, constituted by pharmacy dispensed drug consumption outside the psychiatric hospital sector. An optimized treatment with the use of CYP-test will thus have the consequence that more patients will receive medication at the pharmacy, which is why it is included as increased drug costs in this analysis. In a planning context, it must be expected that the routine use of CYP-test will result in a cost shift from the mental health care sector to the pharmaceutical field. Looking at the effects of the intervention alone, the picture is, however, a picture of a net savings also on the pharmacy dispensed drug consumption, albeit at a modest 1.5 %.

Our study confirms an already established trend of increased costs among the extreme metabolizers. However, the study contributes to our knowledge about the substantial potential savings in the psychiatric treatment of these patients by routine use of CYP-test. It should be kept in mind that the observed savings occur in a study, which has actively promoted the use of CYP-test results. It cannot be expected that the results are trivially transferable to everyday practice.

Overall assessment

This HTA shows, that the CYP2D6 and CYP2C19 metabolizer status (CYP-test) has clinical significance. This is clear from the literature study, which shows that CYP-test can be used to identify patients with an increased risk for the development of antipsychotic drug induced side effects. It is also confirmed by findings of the studies conducted as part of this HTA. Thus, the descriptive studies of the technology section show that CYP2D6 metabolizer status appears as a differentiating factor in the study population. In addition, the economic analysis shows significantly increased expenses in the group of extreme metabolizers, i.e. patients with either poor (PM) or ultra rapid (UM) drug metabolism for either CYP2D6 or CYP2C19. Like the findings in the descriptive studies, this observation suggests that these patients' clinical needs and appearance differs from that of a patient with normal drug metabolizing capacity.

Although an association between CYP metabolizer status and clinical outcome is essential for the use of the CYP-test in clinical routines, it does not necessarily mean that the CYP-test also is useful prospectively as a tool for medical decision making in order to improve clinical outcome in terms of reduced side effects and better efficacy of antipsychotic drug treatment. The trial of the CYP-test as a decision tool in the clinical controlled randomized study shows that the routine use of CYP-test for did not improve treatment persistence, lead to fewer side effects, better efficacy or better compliance. However, it is important to note that the study fails to uncover the potential of the CYP-test completely. This is seen in the economic analysis that shows that the expenses observed in the group of extreme metabolizers are reduced in the study group in which the CYP-test is used to control the antipsychotic drug treatment.

The HTAs organization section points out that there are significant organizational barriers to the efficient use of the CYP-test. Test results are only rarely used for choice of drug and dosage and, according to notes in the patient files, only rarely part of considerations regarding the patient's drug therapy. An effective utilization of the CYP-test requires extensive work to ensure appropriate forums for the exchange of information

and reflection on test use and relevance. It also requires an adaptation of the existing workflow and filing systems to ensure that test answers are visible and easily accessible to the right person at the right time. In addition, it will be essential to increasing physicians' awareness that the test provides a knowledge that may have lifelong relevance to patients' medication. Patients should be better informed about the test result and its possible consequences, and physicians should be made aware of the importance of communicating test result when the patient is discharged.

Thus, despite a number of findings that indicate that the CYP-test has potential for improving antipsychotic drug treatment, it is our opinion that the test in its current state cannot be used as a routine test in psychiatry. Our opinion is primarily based on the significant organizational barriers, but also on the lack of evidence of the test's clinical utility as a tool for improving the antipsychotic treatment.

www.dacehta.dk

The Danish Health and Medicines Authority
Danish Centre for Health Tecnology Assessment (DACEHTA)
Axel Heides Gade 1
2300 København S
Phone no 7222 7400

dacehta@sst.dk
www.dacetha.dk