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RESEARCH REPORTS

Patient preferences for pharmacogenetic screening in depression

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Objectives: The aims of this study were to estimate preferences and willingness-to-pay (WTP) for genetic screening for CYP2D6 polymorphisms among a group of former and currently depressed patients.
Methods: A Web-based discrete choice questionnaire was sent to 89 respondents, age 18–65. Four attributes were included: (i) shifts in antidepressant medication before symptom relief, (ii) time with antidepressant medication without symptom relief, (iii) time with antidepressant medication without symptoms but with adverse side-effects, (iv) cost of genetic screening. We used a switching model with two scenarios, one representing patients' own treatment history and the other a treatment scenario with genetic screening.
Results: In a main-effects model involving the four attributes all coefficients had the expected sign, indicating that as the number of shifts, price or time without symptom relief, and/or dosage-adjustments increased, the likelihood of choosing the screening test decreased. Price and number of shifts in medicine were significant. Marginal WTP for 5 percent probability of a reduction of one in antidepressant shifts was DKK2,599 (€350).
Conclusions: Patients value reductions in shifts in antidepressants and price when choosing between genetic screening and no screening. They do not focus on how the reductions are provided, nor do they value the genetic information the test provides irrespective of its effect on outcome. Given, that the test is able to provide a reduction of one shift in the number of antidepressant shifts with a probability of 5 percent, WTP for the test exceeds its cost.

Keywords: Pharmacogenetics, Depressive disorder, Healthcare economics and organizations, Polymorphism, Genetic

It is assumed that the lifetime risk of developing depression is 10–20 percent (33;37) and the 12-month prevalence is 3–10 percent (44). Depression imposes great burdens on the implicated individuals as well as their relatives and entails a severe decrease in the quality of life, high risk of recurrence as well as suicide (33). The disease is, furthermore, difficult to treat (37), and low response rates to drug therapy as well as high rates of side-effects are well known phenomena (6;25;32). Several studies have estimated the cost-of-illness of depression (2;11;28;40), as well as treatment failure and the cost-consequences of this (31;37;39). Costs are substantial, and even minor improvements in the treatment of depression have the potentials to be cost-saving.

Pharmacogenetic progress within depression has provided a genetic test with the potential to improve treatment.

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Table 1. CYP2D6 Genotype Frequency in a Danish Population and Expected Treatment Response

	Prevalence[a]	If treated with ordinary dosages[b]
Poor metabolizers (PM)	8.4%	High risk of toxicity
Intermediate metabolizers (IM)	8.4%	Increased risk of toxicity
Extensive (normal) metabolizers (EM)	80.1%	Response as expected
Ultra-rapid metabolizers (UM)	3.1%	Decreased chance of effect

[a] See Rasmussen et al. 2006 (35).
[b] Treatment response if treated with substrates that are metabolized by CYP2D6.

The test screens for CYP2D6 polymorphisms, which are changes in genes coding for liver enzymes that metabolizes a substantial part of available antidepressants (and other drugs). It should be emphasized that far from all antidepressants are influenced by CYP2D6. Testing for these polymorphisms is relatively simple and cheap. It requires a single blood sample, and the results are valid for lifetime. The price of having the test in a Danish setting is currently DKK1,630 (€219) (26).

Four genotypes can be identified in which alterations in treatment dosages in concordance with CYP2D6 status are likely to improve treatment response and reduce the risk of adverse side-effects (ADE). These genotypes are shown in Table 1.

Poor metabolizers (PM) do not have the genes coding for the relevant enzymes and will experience increased plasma-concentration levels leading to an increased risk of severe ADEs if treated with (some) antidepressants in ordinary dosages (36). Intermediate metabolizers (IM) have reduced enzymatic activity and will also face an elevated risk of developing ADEs if treated with antidepressants in ordinary dosages (34). Extensive metabolizers (EM) have normal enzymatic activity, while the ultra-rapid metabolizers (UM) have multiple copies of the relevant genes and an increased enzymatic activity. If treated with ordinary dosages UMs are likely not to reach therapeutic plasma concentrations and thereby not obtaining an effect from their pharmaceutical treatment (19;20;23;24).

Measuring the benefits of screening for CYP2D6 polymorphisms is complicated by the fact that not all antidepressants are metabolized by these genes (1;24). Besides, the partly unknown and complex nature of psychiatric diseases complicates the prediction of the response to pharmaceuticals, as this is also affected by individual differences in pathways, receptors, and disease pathology (3;7-9;24). Hence, despite the relatively high prevalence of diverging genotypes, a conservative assumption based on expert opinion is that only 2–5 percent of patients will experience improved treatment effects if genotyped (21). Other studies have argued that future predictive genotyping for metabolizing enzymes in general might benefit somewhere between 15 and 40 percent of drug treatments, although these numbers vary between studies (15;19;22). No larger randomized controlled trials have tested the efficacy of the test yet (30;43), and economic evaluations have only been able to show trends toward cost-effectiveness of genetic testing (10).

Even though the exact effects of using this kind of genetic screening is unknown, its uptake will ultimately depend upon patients' preferences toward it. If the marginal treatment improvements that a genetic test might provide are not valued, it is also doubtable whether large evaluations of the test are worthwhile. Thus, the objective of this study has been to elicit whether patients would value routine screening for CYP2D6 polymorphisms when antidepressants are given for the first time.

METHODS

Patient Recruitment

On the basis of three focus group interviews with former and current patients (published as a working paper) (17), a large Web-based questionnaire was sent out to eighty-nine current or former Danish depressive patients, age 18–65. Recruitment was done through advertisements in an electronic newsletter published from the pharmaceutical company of Lundbeck, who produces antidepressants, as well as on the same company's Web site for depressed people called DepNet. Also, members from the patient association for depressive people in Denmark (Depressionsforeningen) were emailed, if they had agreed to participate in research activity. Posters and flyers with invitations and information about the study were also given at seven different psychiatric wards, but few respondents were recruited this way. Most participants responded to the ad in the newsletter.

Patients were eligible to participate if they had once been diagnosed with an affective disorder and treated pharmacologically for this. No emphasis was put on the specific diagnosis or the number of episodes. Respondents were not rewarded for their participation.

Discrete Choice Experiment

A discrete choice experiment (DCE) was used to elicit patients' preferences for genetic screening. Opposed to conventional cost-effectiveness analyses, a DCE allows all health as well as nonhealth outcomes of a treatment strategy to be included in the analysis (4). In addition, DCEs allow for the relative importance of specified components of the treatment strategy to be calculated. The detailed information is valuable

when new interventions are designed, such that interventions can be tailored to patients' preferences. The results from a DCE can be used in cost-benefit analysis to inform whether a given intervention is welfare improving.

In a DCE, respondents are faced with choices between hypothetical scenarios that differ in terms of specified attributes and levels of these. By varying the levels of the attributes, respondents are forced to make trade-offs, thereby revealing their preferences. The method allows assessments of which incremental changes in attributes that are important, that is, which value components that can explain and affect choices, and the probabilities of choosing a certain scenario, given a marginal change in the levels of the specified attributes, can be estimated. Building on this set of estimated coefficients, the willingness-to-pay (WTP) of both marginal changes in each of the attributes as well as the whole treatment can be calculated.

Design and Analysis

The DCE was conducted as a Web-based questionnaire sent out by an independent research agency (Gallup). Respondents could commence replying, close the questionnaire, and finish later. This option turned out to be a great advantage, as respondents had difficulties maintaining their level of concentration throughout the questionnaire.

The first section of the questionnaire included a description of the genetic test and questions on respondents' attitudes toward genetic screening. This was done to identify respondents with general aversions toward genetic testing not related to the specific context and the attributes of the genetic test in question. Next, questions about the patients' own treatment history, corresponding to the attributes chosen for the choice sets, were posed. The choice sets involved two scenarios, one represented by the patients' own treatment history as a status quo scenario and the other a hypothetical scenario representing treatment with the genetic test. In the literature, this is called a switching model (16). The status quo scenario constitutes an opt-out option. The last part of the questionnaire contained several sociodemographic questions and questions on patients' impressions from their own treatment process.

Focus group interviews, a literature review and expert opinions were used to inform the choice of attributes (17). These are shown in Table 2 and consist of (i) number of shifts in antidepressant medication before symptom relief, (ii) time with antidepressant medication but no symptom relief, (iii) time with antidepressant medication and continuing dosage-adjustments due to ADEs but without symptoms, and (iv) the price of the genetic test. Respondents were told that, on average, the genetic test would not influence their expenses on pharmaceuticals. Levels of the three first attributes were presented as absolute reductions of respectively one or two shifts or 1 or 2 months compared with the status quo alternative. The price attribute had eight levels ranging from DKK200 (€27) to DKK18,000 (€2,420). The price of the test was stated as an out-of-pocket once in a lifetime payment. Respondents were asked to recall the first time they were diagnosed with a depression and asked to choose between the treatment scenario they had already experienced and a hypothetical treatment scenario, where a genetic test with an associated price would be conducted, but where they would only have 5 percent probability of getting any treatment improvements from this, compared with their status quo scenario.

A fractional factorial experimental design optimizing D-efficiency was generated in SAS (27), resulting in a design with thirty-two hypothetical alternatives (the design is available from the authors on request). These thirty-two alternatives were distributed across four blocks of eight while ensuring the maximum degree of orthogonality using the MktBlock macro in SAS. The alternatives were each paired with the respondent's own treatment history (the status quo alternative). The data were analyzed using conditional logistic regression in the statistical software package of STATA version 9.2. Confidence intervals were calculated by bootstrapping with 10,000 replications (5;13;18).

Table 2. Attributes and Levels for These

Attributes	Levels
Number of shifts of antidepressant before symptom relief	Reduction of 1 or 2 shifts
Time period from the pharmaceutical treatment is initiated until the symptoms starts to alleviate (i.e., time before the treatment works)	Reduction of 1 or 2 months
Waiting time with continuing dosage adjustment due to bothering adverse side-effects but without severe symptoms (i.e., before symptom relief)	Reduction of 1 or 2 months
Costs of the genetic test	DKK200 (∼€27) DKK600 DKK1,500 DKK1,800 DKK3,000 DKK6,000 DKK9,000 DKK18,000 (∼€2,420)

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RESULTS

Patient Descriptives

Sixty-five of the eighty-nine respondents completed the questionnaire, giving a response rate of 73 percent. The respondents were on average 41 years old (SD = 11.3). The gender distribution was similar to that of depression, with 70.7 percent women and 29.3 percent men (14). The mean number of years in antidepressant pharmacotherapy was 5 (ranging from 0 to 35), and at the time of the questionnaire 73 percent of the respondents were taking some kind of antidepressant. On average, respondents had had a little more than four shifts in antidepressant medication in their first episode with depression (SD = 3.78). The median waiting time on antidepressant medication before symptom relief in this first sickness episode was 3 months (mean 16 months; SD = 30), which was also the case for the median time with medication, no symptoms but dosage adjustments due to ADEs (mean 10; SD = 17.5). These numbers indicate that the group of respondents is likely to be characterized by having had a moderate to severe depression, or a relatively complicated treatment.

The stated number of shifts in medicine, time before effect, and time with dosage adjustments were less than three for almost half of the respondents. This finding prevented the use of their actual stated number in the status quo scenario as the levels in the alternative with the genetic test would become negative or equal to zero. In these cases, respondents were coded with a *hypothetical* status quo scenario consisting of three shifts in medicine, 3 months without effect, and 3 months with dosage adjustments. In this way, the levels of the hypothetical scenario *with the test* could be applied as intended. Excluding these respondents from the analysis did not affect the results.

Patients' Preferences

Based on a question on respondents' attitudes toward the described genetic test, one nontrader was identified and excluded as he/she did not like the idea of genetic testing and always chose the "no test" scenario. Four respondents had already had the genetic test and were also excluded. As one of the consequences of depression is lack of ability to concentrate, it was expected that for some respondents, the cognitive burden of answering the DCE questions might be too great. Patients were therefore asked how difficult they thought it had been to complete the DCE questions. A 10-point scale was used, where 10 indicated no difficulties. Fifteen respondents stated it had been extremely or very difficult (score < 4) and were excluded. Separate analysis for this group revealed counterintuitive estimates, indicating that respondents had not been able to grasp the meaning of the DCE exercise. Including them increased the variance of the coefficients, but did not alter the overall results.

A conditional logistic regression was run on the final sample of forty-five respondents, who had each completed eight DCE questions. The results are shown in Table 3.

In a main-effects model involving the four attributes as well as a constant representing the genetic test per se, all coefficients had the expected sign, indicating that as the number of shifts, price, time without effect, and/or dosage-adjustments increase, the likelihood of choosing the genetic test decreases. Statistically significant preferences for the number of shifts in antidepressant medicine as well as price was found, while the coefficients on time before symptom relief and time with dosage adjustments after symptom relief did not have a statistically significant effect on preferences. The test itself and the information it provides, irrespective of its effect on the treatment outcome, did not influence respondents' choice. Subgroup analyses did not alter these findings.

Willingness-to-Pay

WTP for each of the attributes is also shown in Table 3, including the 5th and 95th percentiles (90 percent confidence interval). The mean WTP for a 5 percent probability of a reduction of one in the number of shifts in medicine is valued to be DKK2,565 (€345). There is a positive mean WTP for reductions in the time patients have to wait for an effect and for reductions in the time with dosage adjustments. These were however not statistically significant. It was originally hypothesized that the test itself would be of value to

Table 3. Results from a Conditional Logistic Regression with Only Main Effects

Attributes	Coef.	t value	$p > \|t\|$	WTP	5th and 95th percentiles	
Medicine shift	−.4914	−2.08	**0.037**	2,565 DKK	519 DKK	4,867 DKK
Time before effect	−.2603	−1.11	0.269	1,358 DKK	−700 DKK	3,562 DKK
Time with dosage adjustments	−.0522	−0.22	0.825	291 DKK	−1,839 DKK	2,439 DKK
Price of the test	−.0002	−6.92	**0.000**	—	—	—
Constant for test per se	−.2622	−0.43	0.666	−1,372 DKK	−7,099 DKK	3,960 DKK
Model characteristics						
N (respon./observ.)	45/360					
$LL_0/LL_{\text{at convergence}}$	−214.47/−211.29					
LR χ^2 (5)	76.48					
Pseudo R^2	0.1533					

WTP, willingness-to-pay.

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respondents irrespective of its effect on the attributes. This was not found to be the case. The mean WTP for a 5 percent probability of a one-shift reduction in the number of medicine shifts in the first episode of depression is, however, greater than the actual price of the test.

DISCUSSION

The results of this study indicate that depressive patients are willing to pay for improvements in treatment response when treated with antidepressants and that their stated WTP for a 5 percent probability of improvements exceeds the price of a genetic test capable of delivering these. To the extent that the effect of a genetic test is greater, the value of the test will be higher.

No other studies that look at patients' preferences for these kinds of treatment improvements have been conducted. One contingent valuation study was found that looked at patients' preferences for complete recovery from depression (42) and another study was found that looked at patients' WTP for pharmacists' services that reduced risk of medication related problems (41). Results from neither of these studies are, however, comparable to the results presented here.

External Validity

As indicated by the respondents' number of years with depression and the experienced number of shifts in antidepressants, the results from this study is representative for a group of moderately to severely ill patients, probably characterized by a relatively complicated treatment history. This is supported by the fact that the predominant part of respondents was recruited from an information site on depression, despite a broad recruitment strategy. Thus, patients with only minor depressions and/or an uncomplicated treatment history are likely to be underrepresented. Assuming patients with minor or uncomplicated depressions receive treatment in primary care the presented results will primarily be representative of preferences among patients in secondary care, although it is highly unlikely that patients with acute symptoms or recent relapse have had the strengths to participate. This is also indicated by the small number of respondents recruited from psychiatric wards, which also makes it doubtful whether a larger sample size would have improved the generalizability of the findings.

Most respondents were recruited through the Internet, and because the questionnaire was Web-based, this might have prevented some from participating. The use of the Internet and emails is, however, highly frequent in Denmark (12). Those who do not use the Internet are likely to be elderly people (12) and/or represent a group with perhaps a minor aversion toward technological improvements. But as people 65 years of age or older were not included in the study, we do not expect that our recruitment strategy or the Web-based questionnaire has caused any systematic bias.

Internal Validity

We excluded fifteen respondents who stated they had had great difficulties completing the choice task. Inclusion of these respondents resulted in a similar preference pattern but only the coefficient on price were statistically significant at a 5 percent level, and the WTP-estimate for a reduction in number of shifts was reduced to DKK1,512 (SD = 1,045). Among those who had not had difficulties, we tested for respondents' price-sensitivity relative to their stated household income. This test revealed that respondents did consider budget constraints when they chose, indicating that the DCE exercise had been well understood.

Design of the Choice Sets

The genetic test has not to date been tested in larger randomized controlled trials (29), and the range of realistic improvements is unknown (15;43). To the extent that the range in attribute values do not include the true effect of the genetic test, the DCE can be said to be misspecified, and the estimated weightings of the attributes will not necessarily reflect the respondents' preference function. We did however apply conservative estimates in our study and as the WTP exceeds the cost of providing the test, we may consequently conclude that a more effective test must be at least as welfare improving.

The genetic test could be implemented either routinely for all patients whenever antidepressants would be given for the first time, or it could be used only for high-risk individuals in whom treatment difficulties have occurred. The aim of this study was to elicit preferences for the former and it was therefore decided to ask patients to recall their first episode of depression. With an average disease history of 5 years (ranging from 0 to 35 years), this strategy may have introduced recall bias. But, because the choice exercise mainly involves preferences for absolute changes in attribute values across the two alternatives, a potential recall bias is unlikely to have had an effect on choice behavior.

We substituted the patients' own reported attribute levels with values of 3 for each of the treatment attributes, if levels were lower than three. This meant that some respondents were faced with status quo scenarios that did not represent their own situation. Subgroup analyses indicate that this has not introduced bias as preferences did not differ between groups above and below the attribute threshold of three shifts, 3 months, and so on.

The biggest drawback in the conducted DCE is our inability to test whether respondents were sensitive to the probability of 5 percent of getting any treatment improvements from the test. We did consider including a fifth attribute representing the probability of belonging to one of the deviant genotypes and getting an improved treatment effect from the genetic test. The theoretically realistic levels of such an attribute could either have been lower than the 5 percent or slightly higher, for example, 10 percent. However, studies

have shown that respondents have difficulties distinguishing between probabilities when these are in the lower range (38). We also judged that inclusion of an additional variable might increase respondents' cognitive burden significantly and potentially sacrifice statistical power. Unfortunately, the lack of variation in probability levels means we have not been able to test whether respondents considered the probability of gain, when choosing between the scenarios. The concept of probability was, however, carefully explained in the description of the test and the level of probability was carefully highlighted in each choice set to attract attention to this important characteristic.

Payment Vehicle

More than 80 percent of respondents had paid for psychological sessions themselves, with a median number of twelve sessions (something not offered free of charge in the Danish health care system). In addition, only half of the patients had spent less than DKK3,500 (€470) out-of-pocket on antidepressant medication within the past year, while 17 percent of respondents had spent more than DKK9,500 (€1,280) (pharmaceuticals are only partly subsidized in the Danish health care system). These numbers indicate that respondents, as patients, are accustomed to paying for treatment themselves and that there should not be severe problems related to the direct out-of-pocket payment vehicle used in this DCE, despite the primarily tax-financed Danish healthcare system.

Patients' Preferences for Treatment Improvements

We were not able to demonstrate a statistically significant relationship between choices and the different levels of the two attributes related to time. Several possible reasons for this exist. First, the sample is not very big, and with the limited number of observations, it may not be possible to detect an effect. Second, the levels of reductions in time may not have been large enough to make an impact on choice patterns. Our sample consisted of predominantly long-term ill patients, which means they have already experienced many "waits" in their history as patients and a reduction of 1–2 months may seem trivial to them. Third, it might be that respondents did not fully understand the attributes or they implicitly associated an increased number of shifts with the time attributes, thus, ignoring the improvements in "waiting time" independent of a reduction in number of shifts.

A close substitute of the genetic test exists in the shape of therapeutic drug monitoring (TDM). TDM is capable of delivering the same treatment improvements as the genetic test if used on a routine basis. Our results show that respondents value the outcomes associated with the genetic test, but not the test per se. Hence, TDM may be valued equally highly if it can provide patients with the same improvements in treatment. To the extent that TDM is a close substitute to the genetic test, the demand for genetic testing observed in the present study may not reflect demand in real life if TDM is an option.

CONCLUSIONS

In a DCE conducted among a group of former and current moderately to severely depressed patients, we found that the primary drivers of patient preferences for a genetic test investigating patients' ability to metabolize antidepressants were reductions in the number of medicine shifts and price. No utility was associated with the test per se. The strong preferences for reductions in number of shifts in antidepressants suggests that patients may be highly frustrated with additional shifts and much less troubled by the waiting time for symptom relief and reductions in side effects once they are on a specific medication. This may not always be realized by prescribers when they choose to test another pharmaceutical as opposed to looking at patients' metabolizing capacity. Our results indicate that the genetic test is of value to patients if there is a small probability of obtaining reductions in shifts, but also that other methods that can generate the same level outcome—such as therapeutic drug monitoring used in a routine manner—is likely to be of the same value.

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