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Drug attitude as predictor for effectiveness in first-episode schizophrenia: Results of an open randomized trial (EUFEST)

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for the EUFEST Study Group

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We thank all patients who participated in the study.

Contributions

All authors contributed equally to and have approved the final manuscript.
Abstract

Objective: Effectiveness has become more and more important as a comprehensive outcome measure for (long-term) treatment in schizophrenia. Early predictors to identify patients at a high risk for not succeeding the initiated treatment would be very useful. Discontinuation of the initiated treatment was used as criterion for effectiveness and patients' drug attitude was shown to be predictive for non-adherence or discontinuation of long-term treatment in schizophrenia. Accordingly, the predictive validity of the Drug Attitude Inventory (DAI) for effectiveness should be evaluated.

Methods: Based on a sub-sample of patients from the EUFEST study for whom DAI assessments were available significant predictors for effectiveness as measured by discontinuation of initiated treatment were identified based on a logistic and a Cox-regression analysis. A Receiver Operating Characteristic (ROC-) analysis was conducted for the DAI, prognostic / diagnostic parameters (sensitivity, specificity) were calculated and a cut-off value suggested.

Results: In a sample of 228 first-episode patients, DAI scores were the most powerful predictor for effectiveness (p<0.001) besides two other significant predictors (PANSS-positive score and sexual side effects). The ROC-analysis revealed an area under the curve of 0.64 (p<0.001). The suggested cut-off point of about 20 yielded a sensitivity of 70-75% and a specificity of 40-45%.

Conclusions: Study results indicate that the Drug Attitude Inventory, filled in by patients early in treatment seems to be a valid predictor for effectiveness as measured by discontinuation of the initiated treatment. DAI scores could also serve as a (differential) indicator for the need of enhanced treatment monitoring. These findings have to be validated in other (first-episode) samples.
Key words

Schizophrenia, first episode, effectiveness, treatment discontinuation, drug attitude, predictor
Introduction

In recent years, the concept of 'effectiveness' (e.g. Hogarty et al 1997) has become crucial regarding the evaluation of long-term drug treatment in schizophrenia (Fleischhacker et al. 2005, Lieberman et al. 2005, Kahn et al. 2008). As a pragmatic comprehensive measure, it integrates aspects of efficacy, safety, and tolerability and considers both, the perspective of the patient and the clinician. In general, the rates of retention or (dis-) continuation serve as an appropriate indicator reflecting all of these parameters. Since non-adherence or drug discontinuation is a critical issue in the long-term treatment of schizophrenia, considerable effort has been made to identify early indicators and to provide interventions to keep patients in an (in general) effective and safe treatment. Patients' attitude towards drug treatment has emerged as one of the factors associated with drug-discontinuation or non-adherence (Lacroet al. 2002), so it could be assumed, that it might be a predictor for 'effectiveness' as well. This hypothesis was tested by analyzing data from the European First-Episode Schizophrenia Trial (EUFEST; Fleischhacker et al. 2005, Kahn et al. 2008).

In recent years, several studies have identified predictors for treatment discontinuation or non-adherence in first-episode patients (Verdoux et al. 2000, Kampman et al. 2002, Robinson et al. 2002, Mutsatsa et al. 2003, Perkins et al. 2006, De Haan et al. 2007, Perkins et al. 2008, Rabinovitch et al. 2009, Miller et al. 2009). The indicators included and extracted are as manifold as in multiple episode patients: lower occupational status, substance abuse, psychopathology (more pronounced delusional symptoms and suspiciousness; Verdoux et al. 2000), negative attitudes toward drug treatment and lack of insight (Kampmann et al. 2002, Mutsatsa et al. 2003), poor premorbid (cognitive) and post-acute (executive) functioning, more pronounced (extrapyramidal) side effects (Robinson et al. 2002, Perkins et al. 2008), lower expectations regarding the need for or effectiveness of general or drug-specific treatment, treatment with first (vs. second) generation antipsychotics (FGAs / SGAs; Perkins et al. 2006), hostility and uncooperativeness, involuntary admission (De Haan et al. 2007),
poor treatment response, low adherence to preceding treatment, poor cognitive functioning, persisting negative or depressive symptoms, ethnicity (Perkins et al. 2008), less social support, living alone, refusing drugs at treatment initiation (Rabinovitch et al. 2009), and substance abuse (Perkins et al. 2008, Miller et al. 2009).

Based on theoretical considerations (Perkins 2002, Weiden 2007) and empirical findings, patients' attitude towards drug treatment was suggested to be a factor associated with treatment discontinuation both in unselected samples (mainly multiple episode patients; Lacro et al. 2002) and in first-episode patients (Kampman et al. 2002, Mutsatsa 2003, Perkins et al. 2006, 2008). Several scales have been developed for an easy and valid assessment of such attitudes (e.g. Hogan et al. 1983, McEvoy et al. 1989, Weiden et al. 1994, Kampman et al. 2000, Dolder et al. 2004). The Drug Attitude Inventory (DAI) by Hogan, Awad and colleagues (1983) is one of the earliest developed and most widely used scale. Patients are asked to answer 30 dichotomous items (or 10 items in the short form), reflecting various positive and negative attitudes to drug treatment. These can be summarized to an overall composite score (Hogan et al. 1983).

The main objective of this paper is to examine the predictive validity of the DAI (30 items form) regarding effectiveness in first-episode patients, as measured by discontinuation of the initiated treatment for any reason. In addition, (other) predictors for effectiveness of long-term maintenance treatment in first-episode schizophrenia aimed to be identified.

Methods
Study setting, patients and design
The analyzed data derived from EUFEST in which the FGA haloperidol was compared with
four SGAs (amisulpride, olanzapine, quetiapine, ziprasidone; open randomized design) in
first-episode patients with schizophrenia spectrum disorders regarding differences in
effectiveness (i.e. drug discontinuation; see below). Detailed study characteristics have been
described elsewhere (Fleischhacker et al. 2005, Kahn et al. 2008). A total of 50 centers
participated in 13 European countries and in Israel. Eligible patients were 18-40 years of age
and met DSM-IV criteria for schizophrenia, schizotypal, or schizoaffective disorder
confirmed by the Mini International Neuropsychiatric Interview Plus (MINI+; Sheehan et al.
1998). Patients were excluded if: (1) more than two years had passed since the onset of
positive symptoms; (2) any antipsychotic had been used exceeding two weeks in the previous
year or six weeks lifetime; (3) patients had a known intolerance to one of the study drugs; (4)
patients met any of the contraindications for any of the study drugs as mentioned in the (local)
package insert texts.

Patients were included after written informed consent was obtained following a complete
description of the study. The trial complied with the Declaration of Helsinki and was
approved by the ethics committees of the participating centers.

Patients were randomized to: haloperidol 1-4 mg/d, amisulpride 200-800 mg/d, olanzapine 5-
20 mg/d, quetiapine 200-750 mg/d, or ziprasidone 40-160 mg/d. All study medications were
administered orally within the approved dose ranges at the treating physician’s discretion.

Data were collected at baseline (between four weeks before and one week after
randomization) and after 0.5, 1, 1.5, 2, 3, 6, 9, and 12 months. Assessments included data on
demographics, diagnosis, psychopathology [PANSS (Kay et al. 1986), CGI (Guy 1976),
CDSS (Addington et al. 1990)], side effects [St Hans rating scale; SHRS (Gerlach et al.
1993), UKU-sexual dysfunctions (Scandinavian Society of Psychopharmacology 1987)],
quality of life [MANS A (Priebe et al. 1999)], compliance (CRS; Kemp & Hayward 1996), and attitude toward drugs (DAI; Hogan et al. 1983).

Effectiveness i.e. discontinuation of the initiated treatment was defined as: (1) the use of a dose below the predefined range including complete discontinuation; (2) the use of a dose greater than the predefined range (3) the use of another antipsychotic drug—each for more than 14 days over 6 months; or (4) the use of any parenteral antipsychotic drug when the drug was active for more than 14 days over 6 months. The reason for treatment discontinuation was noted.

Statistical methods
Predictors for effectiveness as the (dichotomous) dependent variable were identified based on a logistic and a Cox-regression analysis (including time to discontinuation as the dependent variable). Potential predictors initially considered (all assessed at baseline) included: age, gender, years of education (years in school following the age of 6), highest degree of education (from 1='university completed' to 7='less than high school'), currently employed (yes/no), married (yes/no), living alone (yes/no), substance abuse / dependence (yes/no according to MINI-plus diagnostic interview), duration of psychosis (months; based on interviewers estimate of onset of full syndrome), antipsychotic naïve (yes/no), PANSS-positive, -negative and -general-score, illness severity (CGI-S), depression (CDSS), akathisia, dystonia, parkinsonism and dyskinesia (all 'yes/no' according to SHRS), sexual side effects (yes/no according to UKU-sexual dysfunction sub-scale), quality of life (MANSA), compliance rating (CRS), and drug attitude (DAI-30). A stepwise forward selection algorithm was applied with a 5%-significance limit for inclusion. Since general predictors for effectiveness independent of drug treatment should be identified, the drug group was included
as a 'strata' variable. Thus, the drug group effects were considered in the model and the resulting parameters were adjusted for it.

The prognostic validity of the DAI was assessed with a Receiver-Operating-Characteristic-(ROC-) analysis (Hsiao et al. 1989). By varying the cut-off-points of the distribution of the DAI-scores, different sensitivity and specificity values were obtained, leading to a specific curve. The area under the curve (AUC) was compared with a curve obtained by chance with a Wilcoxon statistic. Finally, optimal cut-off-points were discussed. Statistical analyses were conducted with SPSS statistical package, version 15.

Results

Sample characteristics

The entire EUFEST sample consisted of 498 patients (haloperidol / hal: n=103 / 20.7%; amisulpride / ami: n=104 / 20.9%; olanzapine / ola: n=105 / 21.1%; quetiapine / quet: 104 / 20.9%; ziprasidone / zipra: n=82 / 16.5%), of whom 232 (46.6%) patients had DAI-assessments and could be entered into this analyses. Four patients had to be excluded from the predictor specific analysis due to missing values in one or more of the parameters. Accordingly, the analysis includes n=228 patients (hal: n=43 / 18.9%; ami: n=47 / 20.6%; ola: n=53 / 23.2%; quet: 52 / 22.8%; zipra: n=33 / 14.5%). Comparing the entire original sample (n=498) with the sample used for this sub-analysis (n=228) yielded no significant differences with regard to proportion of drug group assignment, drug group specific discontinuation rates, (primary sample: hal=61.2%; ami=30.8%; ola=28.6%; quet=49.0%; zipra=37.8%; predictor sample: hal=67.4%; ami=40.4; ola=39.6; quet=53.8; zipra=39.4), gender, age, diagnostic
group, prior drug treatment as well as mean PANSS-positive, -negative and -general scores, and quality-of-life (MANSA; all p>0.15).

The mean age of the 228 patients was 25.6 years (SD=5.4), and 124 (54.4%) were male. The proportion of a diagnosis of schizophrenia, schizophreniform and schizoaffective disorder was 52.2% (n=119), 40.4% (n=92) and 7.5% (n=17) respectively; 71 (31.1%) of the patients were drug-naïve. Treatment discontinuation for any reason was observed in 110 patients (48.2%) after a mean of 3.1 months (sd=3.1; median=2.1).

**Differences between patients who discontinued and those who completed: identified predictors for effectiveness**

At baseline, patients who discontinued differed from those who completed as follows (see also Table 1): Patients who discontinued the randomized drug treatment within the 12-month observation period had a lower PANSS-positive score (p=0.01) and a lower score on the drug attitude inventory (DAI; p<0.001). In addition, the following differences reached borderline significance level (0.05<p<0.15): patients who discontinued were younger (p=0.14), had a longer illness duration (p=0.08), a lower PANSS-general score (p=0.12), had more akathisia (p=0.08) and sexual side effects (p=0.15).

(Insert Table 1 about here)

The logistic regression analysis yielded the following significant predictors based on a stepwise forward selection: drug attitude (odds ratio / 'OR' = 0.95; 95%-CI: 0.93; 0.98; p<0.001) and PANSS-positive score (OR = 0.91; 95%-CI: 0.86; 0.97; p=0.002). Based on a Cox-regression analysis the following predictors for time to discontinuation were selected:
drug attitude (hazard ratio / 'HR' = 0.96; 95%-CI: 0.95; 0.98; p<0.001) and sexual side effects (according to UKU; HR = 0.63; 95%-CI: 0.42; 0.97; p=0.04).

**Prognostic validity of the Drug Attitude Inventory (DAI)**

The ROC-analysis of the Drug Attitude Inventory regarding effectiveness yielded an AUC=0.64 which is significantly different from a curve obtained by chance (p<0.001, Figure 1).

(Insert Figure 1 about here)

Table 2 gives sensitivity and specificity parameters for selected DAI cut-off-points. A low cut-off point of <=8 vs. >=10 (patients with scores of 8 and below will be classified / predicted as 'discontinued' while 9 and above as 'completed') results in a sensitivity of 42.7% (i.e. percentage of patients correctly predicted as discontinued from all patients discontinued) and a specificity of 82.2% (i.e. rate of patients correctly predicted as completers from all completers). With increasing cut-off scores, sensitivity increases, however specificity declines.

Based on the following considerations, an 'optimal' cut-off point will be suggested: the primary aim is to predict / detect patients at high risk for discontinuing the initiated treatment (preferred high sensitivity) in order to be able to initiate prophylactic interventions (for instance enhanced monitoring or even more specific measures such as compliance management). On the other hand 'costs' should be minimized (i.e. not to initiate the intervention too often what means that not too many patients overall are below the cut-off-score) and in particularly to provide the intervention only for those for whom it will be indicated (preferred high specificity). In this respect, a DAI cut-off around 20 seems
appropriate, resulting in a sensitivity of 70-75%, a specificity of 40-45%, and a rate of 60-65% from all patients who have a score below the cut-off.

(Insert Table 2 about here)

**Discussion**

Since effectiveness has increasingly been used as an important outcome in schizophrenia, it was aimed to investigate the predictive validity of the Drug Attitude Inventory (DAI) in this purpose.

Data derived from the European First Episode Schizophrenia Trial (EUFEST; Fleischhacker et al. 2005, Kahn et al. 2008), an open randomized controlled trial comparing four SGAs with the FGA haloperidol over one year regarding differences in effectiveness in patients suffering from their first psychotic illness episode.

Out of 23 parameters assessed at baseline and included as potential predictors in a logistic and a Cox-regression analysis, the patients’ attitude toward drugs assessed by the Drug Attitude Inventory (DAI) consistently resulted as the strongest predictor for effectiveness (i.e. discontinuation of initiated treatment; p<0.001). This corresponds to other studies, in which drug attitude was found as a predictor for drug non-adherence or discontinuation in unselected samples comprising of mainly multiple episode schizophrenia patients (4) as well as in specific samples of first-episode patients (Kampman et al. 2002, Mutsatsa 2003, Perkins et al. 2006, 2008; in the latter of borderline significance). In the sample analyzed here, only one additional significant predictor evolved, depending on the method applied (a lower PANSS-
positive score in the logistic regression analysis; p=0.002; sexual side effects as measured by UKU in the Cox-regression analysis; p=0.04).

In addition, it was aimed to examine the predictive validity of the DAI regarding effectiveness (Sackett and Haynes 2002). Therefore, a Receiver-Operator-Characteristic- (ROC-) analysis was conducted which yielded an area under the curve (AUC) of 0.64, which is significantly different from a curve obtained by chance (p<0.001). This, to our best knowledge, is the first time that the predictive validity of the DAI for effectiveness was tested with this method. Different values for sensitivity and specificity resulted, depending on DAI cut-off scores. In order to predict / detect as many as possible patients at high risk for discontinuation sensitivity should be maximized. On the other hand the false-positive rate should be as small as possible to ensure that potential measures to prevent treatment discontinuation will not be applied to patients who are not in need of it. Thus, we suggest a cut-off-point for the DAI of around 20 which would result in a sensitivity of about 70-75% (rate of correctly predicted discontinuing patients) and a specificity of about 40-45%. This would entail that in 60-65% of all patients, such an intervention would be provided.

Even if there are no other studies regarding predictive / diagnostic validity of predictors for effectiveness (or discontinuation; to our best knowledge) to which our results could be compared one would expect or wish better parameters. Nevertheless, the DAI is an easy to use and valid instrument which provides empirically based support regarding the identification of patients at risk to discontinue initiated treatment. In addition, the analyses were conducted in one of the largest first episode samples studied in this context, with appreciable numbers of antipsychotic-naïve patients.
All these results have to be discussed against some limitations. First, a substantial proportion of the entire EUFEST sample (about 50%) did not complete the DAI and therefore could not be included in this analysis. This might have led to a positive selection of patients with regard to the willingness to cooperate and to comply. However, we have compared the total original sample and the 'predictor' sample analyzed here regarding various clinical and demographic variables (including age, gender, drug assignment, discontinuation rate, diagnosis, duration of psychotic illness, pre-treatment, and psychopathology) and no significant differences evolved (all significance levels for differences were above 0.15). This might indicate that sample selection has not biased results.

Secondly, generalizability is restricted as identified predictors and parameters have been optimized for this sample and need to be validated in independent samples.

**Conclusions**

Study results indicate that the Drug Attitude Inventory completed by patients early in long-term treatment appears to be a useful predictor for effectiveness as measured by discontinuation of the initiated treatment and could serve as a (differential) indicator to initiate specific measures like enhanced monitoring or compliance enhancing interventions. These findings have to be validated in other first-episode samples including measures to enhance the predictive validity.
Steering Committee


Acknowledgement

The authors thank Georg Kemmler for giving statistical advice.
References


Table 1: Characteristics of patients, differences between those who completed or discontinued initiated drug treatment within the 12-months treatment phase.

<table>
<thead>
<tr>
<th></th>
<th>Total (N= 228)</th>
<th>Completed (n= 118)</th>
<th>Discontinued (n= 110)</th>
<th>p&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years; mean; SD)</strong></td>
<td>25.6 5.4</td>
<td>26.1 5.6</td>
<td>25.0 5.2</td>
<td>(0.14)</td>
</tr>
<tr>
<td><strong>Gender (male; N, %)</strong></td>
<td>124 54.4</td>
<td>67 56.8</td>
<td>57 51.8</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Years of education (mean, SD)</strong></td>
<td>12.8 2.8</td>
<td>13.0 2.9</td>
<td>12.5 2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Highest degree of education (mean, SD)</strong></td>
<td>4.1 2.0</td>
<td>4.0 2.1</td>
<td>4.1 1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Currently employed (N; %)</strong></td>
<td>101 44.3</td>
<td>55 46.6</td>
<td>46 41.8</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Married (N; %)</strong></td>
<td>23 10.1</td>
<td>13 11.0</td>
<td>10 9.1</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Living alone (N; %)</strong></td>
<td>21 9.2</td>
<td>11 9.3</td>
<td>10 9.1</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Substance abuse / dependence (N; %)</strong></td>
<td>47 20.6</td>
<td>21 17.8</td>
<td>26 23.6</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Duration of psychosis (mean; SD)</strong></td>
<td>4.2 8.5</td>
<td>3.0 3.4</td>
<td>5.5 11.5</td>
<td>(0.08)</td>
</tr>
<tr>
<td><strong>Antipsychotic naïve (N; %)</strong></td>
<td>71 31.1</td>
<td>37 31.4</td>
<td>34 30.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>PANSS (mean; SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Positive-score</td>
<td>23.3 5.9</td>
<td>24.3 5.6</td>
<td>22.3 5.9</td>
<td>0.01</td>
</tr>
<tr>
<td>- Negative score</td>
<td>21.1 7.6</td>
<td>21.5 6.8</td>
<td>20.7 8.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>- General-score</td>
<td>44.8 10.3</td>
<td>45.9 10.0</td>
<td>43.7 10.6</td>
<td>(0.12)</td>
</tr>
<tr>
<td><strong>CGI: illness severity (mean; SD)</strong></td>
<td>4.9 0.7</td>
<td>4.9 0.7</td>
<td>5.0 0.8</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Depression (CDSS; mean; SD)</strong></td>
<td>5.4 5.2</td>
<td>5.3 5.6</td>
<td>5.4 4.8</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Extrapyramidal side effects (SHRS; N; %)</strong></td>
<td>21 9.2</td>
<td>7 5.9</td>
<td>14 12.7</td>
<td>(0.08)</td>
</tr>
<tr>
<td>- Akathisia</td>
<td>5 2.2</td>
<td>2 1.7</td>
<td>3 2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>- Dystonia</td>
<td>22 9.6</td>
<td>9 7.6</td>
<td>13 11.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>- Parkinsonism</td>
<td>1 0.4</td>
<td>0 0.0</td>
<td>1 0.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Sexual side effects (UKU; mean; SD)</strong></td>
<td>59 25.9</td>
<td>26 22.0</td>
<td>33 30.0</td>
<td>(0.15)</td>
</tr>
<tr>
<td><strong>Quality of life (MANSA; mean; SD)</strong></td>
<td>4.0 0.9</td>
<td>4.0 0.9</td>
<td>4.0 0.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Compliance (CRS; mean; SD)</strong></td>
<td>5.5 1.2</td>
<td>5.6 1.2</td>
<td>5.5 1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Drug attitude (DAI; mean; SD)</strong></td>
<td>13.9 11.7</td>
<td>17.0 9.5</td>
<td>10.7 12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Randomised study medication (N; %)</strong></td>
<td>43 18.9</td>
<td>14 11.9</td>
<td>29 26.4</td>
<td>0.03</td>
</tr>
<tr>
<td>- Haloperidol</td>
<td>47 20.6</td>
<td>28 23.7</td>
<td>19 17.3</td>
<td></td>
</tr>
<tr>
<td>- Amisulpride</td>
<td>53 23.2</td>
<td>32 27.1</td>
<td>21 19.1</td>
<td></td>
</tr>
<tr>
<td>- Olanzapine</td>
<td>52 22.8</td>
<td>24 20.3</td>
<td>28 25.5</td>
<td></td>
</tr>
<tr>
<td>- Quetiapine</td>
<td>33 14.5</td>
<td>20 16.9</td>
<td>13 11.8</td>
<td></td>
</tr>
</tbody>
</table>

1 Significance level for testing differences between 'Completed' and 'Discontinued'; categorical variables: Chi-square-test or Fishers exact test for small cell frequencies; continuous variables: Mann-Whitney-Test, since at least one of the pre-conditions for a t-test (homogeneity of variances; normal distribution) was not fulfilled; p-values between 0.05 and 0.15 were given in parentheses; n.s.: p>0.15.
Figure 1: ROC-curve of the Drug Attitude Inventory regarding effectiveness / drug discontinuation (AUC=0.64; p<0.001)
Table 2: Sensitivity and Specificity regarding effectiveness for different cut-off-points of the Drug Attitude Inventory

<table>
<thead>
<tr>
<th>Cut-off for DAI</th>
<th>TP</th>
<th>Sensitivity</th>
<th>TN</th>
<th>Specificity</th>
<th>% &lt;=Cut-Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=8 vs. &gt;=10</td>
<td>47</td>
<td>42.7</td>
<td>97</td>
<td>82.2</td>
<td>29.8</td>
</tr>
<tr>
<td>&lt;=10 vs. &gt;=12</td>
<td>47</td>
<td>42.7</td>
<td>92</td>
<td>78.0</td>
<td>32.0</td>
</tr>
<tr>
<td>&lt;=12 vs. &gt;=14</td>
<td>51</td>
<td>46.4</td>
<td>83</td>
<td>70.3</td>
<td>37.7</td>
</tr>
<tr>
<td>&lt;=14 vs. &gt;=16</td>
<td>57</td>
<td>51.8</td>
<td>76</td>
<td>64.4</td>
<td>43.4</td>
</tr>
<tr>
<td>&lt;=16 vs. &gt;=18</td>
<td>66</td>
<td>60.0</td>
<td>63</td>
<td>53.4</td>
<td>53.1</td>
</tr>
<tr>
<td>&lt;=18 vs. &gt;=20</td>
<td>76</td>
<td>69.1</td>
<td>55</td>
<td>46.6</td>
<td>61.0</td>
</tr>
<tr>
<td>&lt;=20 vs. &gt;=22</td>
<td>84</td>
<td>76.4</td>
<td>48</td>
<td>40.7</td>
<td>67.5</td>
</tr>
<tr>
<td>&lt;=22 vs. &gt;=24</td>
<td>88</td>
<td>80.0</td>
<td>35</td>
<td>29.7</td>
<td>75.0</td>
</tr>
<tr>
<td>&lt;=24 vs. &gt;=26</td>
<td>98</td>
<td>89.1</td>
<td>25</td>
<td>21.2</td>
<td>83.8</td>
</tr>
</tbody>
</table>

1 The distribution of the DAI-scores (almost exclusively even numbers) results from the scoring procedure for the DAI total score
2 Frequency 'true positives' ('discontinued' and DAI <= lower cut off)
3 Rate (%) of TP from all patients 'discontinued' (N=110)
4 Frequency 'true negatives' ('completed' and DAI >= upper cut off)
5 Rate (%) of TN from all patients 'completed' (N=118)
6 Rate (%) with a DAI-score <= lower cut off from all patients (N=228)