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Identifying the profile of optimal candidates for antipsychotic depot therapy
A cluster analysis

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ABSTRACT

Objective: The prescription rate of antipsychotic depots for patients suffering from schizophrenia is currently low. Among these patients the assumable acceptance rate of depot as treatment of choice is markedly higher, but psychiatrists do report that patients frequently reject the offer of depot treatment. In a first step to highlight this contradiction we aimed at identifying attributes of patients that indicate their qualification for depot treatment in the eyes of the psychiatrists.
Method: We surveyed 201 psychiatrists about their evaluation of patients' attributes potentially influencing their qualification for depot treatment. Multidimensional and cluster analyses were applied to detect associated attributes. A second sample of further 248 psychiatrists was asked about their proposal of depot treatment to patients depending on the number of relapses in the past.
Results: Two clusters of attributes were identified characterizing patients' qualification for depot treatment. In cluster I episodes of non-compliance and relapses in the past were considered as favoring the qualification. cluster II included a high level of insight, openness to drug treatment and profound knowledge about the disease representing attributes that increase patients' qualification. Patients were significantly more likely to be offered depot treatment after their fourth reexacerbation compared to their first relapse.
Conclusions: Attributes comprised in cluster I highly qualify a patient for depot treatment which is in line with the current prescription stereotype. This conservative notion of depot use is supplemented by an alternative cluster II patient profile. Patients fitting this cluster also potentially qualify for depot treatment according to the surveyed psychiatrists and should be offered depot in clinical routine considering the advantages of this form of administration.

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1. Introduction

The advantages of antipsychotic depot treatment in the relapse prevention of schizophrenia have been demonstrated for first generation antipsychotics (FGA) in several studies done since their development in the 1960s, showing both diminished rates and reduced durations of rehospitalization (Davis et al., 1994). Current clinical trials (Simpson et al., 2006; Medori et al., 2008; Chue et al., 2005) corroborate these findings and the advantages prove robust even when the outcome of FGA depot treatment is compared to oral second generation antipsychotics (SGA) in naturalistic studies (Tiihonen et al., 2006). With the introduction of oral SGAs, however, prescription rates of depot formulations decreased, probably because psychiatrists wanted their patients to benefit from the potential advantages of SGAs (Patel and David, 2005).

In a recent survey the participating psychiatrists reported that they have offered antipsychotic (FGA or SGA) depot treatment to only 35% of their patients suffering from schizophrenia or schizoaffective disorder (Heres et al., 2006). The reasons why two thirds of the patients have never been offered depot treatment are yet speculative. Although the overall acceptance of depot treatment among patients with schizophrenia (Heres et al., 2007) is considerably higher, the current depot prescription rate does not even reach 20% in most countries (Nasrallah, 2007; Sim et al., 2004; Ahn et al., 2008). In addition, psychiatrists quote the patients' refusal of depot treatment as one of the most frequent reasons for not prescribing a depot (Heres et al., 2006). We hypothesize that only a small number of those patients generally willing to consider depot treatment for relapse prevention are represented in the group of patients who are in fact offered depot treatment by their psychiatrists.

In a first step to highlight this discrepancy we aim to characterize those patients who are qualifying for depot treatment in the eyes of the psychiatrists. Based on their individual prescription practice the psychiatrists were asked to rate patients' attributes as to how they are representing the qualification for depot treatment. As psychiatrists tend to overestimate compliance with antipsychotic treatment and assume low levels of depot acceptance in their own patients compared to patients in general (Byerly et al., 2002; Heres et al., 2006, 2007) we included additional questions to further investigate these supposed discrepancies.

Despite the fact that second generation antipsychotics have advantages compared to conventional drugs (Leucht et al., 2003; Correll et al., 2004), we saw little differences regarding depot prescription practice between the two classes in a recent survey (Heres et al., 2006). Thus we did not differ between FGA and SGA depot drugs as the depot treatment approach itself regardless of the antipsychotic class was the focus of our analysis. Depot formulations of both antipsychotic classes are available for prescription in Germany.

2. Methods

At an international conference in Germany in November 2006 psychiatrists attending two independently arranged symposia (sample A and B) were surveyed with two questionnaires. We decided to survey two independent samples of psychiatrists because the questions in the two surveys were considered to interact (Fig. 1). The conference comprised symposia on various psychiatric diseases. The participants of our survey were German speaking.

2.1. Questionnaire of sample A — patients' attributes and level of non-compliance

Participants of sample A were requested to state how many of their patients suffering from schizophrenia were currently receiving antipsychotic depot treatment and how many were being treated with a second generation antipsychotic in oral or depot formulation. The psychiatrists were further asked to rate to what extent fourteen different attributes of patients suffering from schizophrenia do influence their qualification for antipsychotic depot treatment based on their individual prescription practice. The fourteen attributes, partly deriving from earlier studies on the decisional process of psychiatrists (Hamann et al., 2005) were selected by the authors based on consensus, pre-tested by 20 psychiatrists in a clinic in Munich, Germany, and revised. The degree of influence was rated on an eleven-point-scale ranging from "0=not qualifying for depot treatment" to "10=highly qualifying for depot treatment." If the participants felt that

an attribute did not influence the qualification of a patient for depot treatment, they were able to choose the option "no influence on the qualification for antipsychotic depot treatment" alternatively. Additionally the psychiatrists appraised the percentage of their patients currently on oral antipsychotics having ever been offered depot treatment by them. Finally the participants were asked to estimate alternatively how many of their own patients (version A1) or how many of all patients in Germany (version A2) suffering from schizophrenia do presumably not take their antipsychotic medication as prescribed. We hypothesized that the participants will underestimate noncompliance in their own patients more clearly than in patients in general. The assignment of the two versions (version A1 or A2) of the last question to the participants was random.

2.2. Questionnaire of sample B — depot acceptance and depot proposal

The assignment of the two versions of the questionnaire (version B1 or B2) to the participants in sample B was random. Participants were either asked to estimate how many of their own patients (version B1) or how many of all patients in Germany (version B2) suffering from schizophrenia would accept antipsychotic depot treatment. We hypothesized that psychiatrists might view their own patients to be less open to depot treatment than patients in general. This assumption is based on a finding from an earlier study in which participants reported the refusal of depot proposal (FGA or SGA) as a major obstacle for depot prescription (Heres et al., 2006). Furthermore participants were asked to rate how likely it would be for them to propose depot treatment to a patient either after the first schizophrenic reexacerbation (version B1) or after the fourth relapse (version B2). We assumed that not only the given fact of a relapse in the past plays a role in depot recommendation but also the number of previous relapses. Scoring was done on an 11-point scale ranging from "0=very unlikely" to "10=very likely."

Both questionnaires included items on demographic data of the participants as well as questions on antipsychotic depot treatment. Demographic data covered the age of the psychiatrist, gender, length of experience in psychiatry, type of institution and official position at the institution. Furthermore, each psychiatrist was to estimate how many patients with a diagnosis of schizophrenia or schizoaffective disorder she/he had treated in the year 2006.

2.3. Statistical analysis

The fourteen attributes in the questionnaire of sample A concerning the qualification for depot treatment are presented as means and standard deviations. Attributes rated in a similar manner can
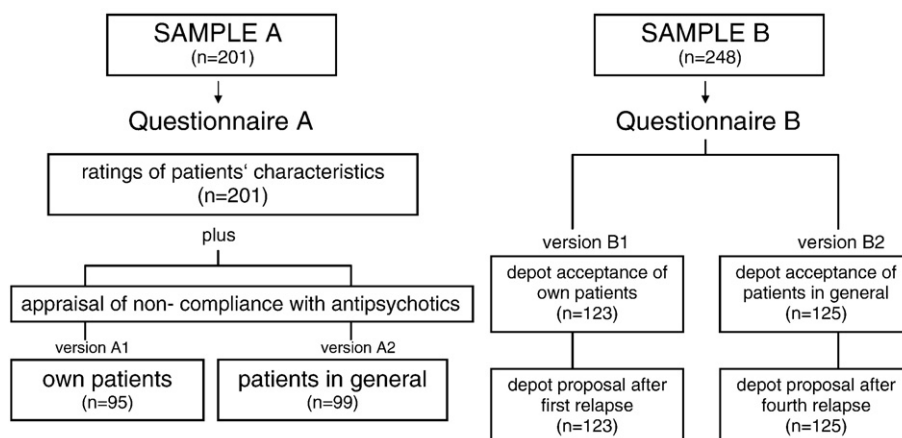

Fig. 1. Types of questionnaires used in the study and corresponding sample sizes.

Table 1
Demographics of samples A and B

		Sample A	Sample B
		n (%)	*n* (%)
Gender: female/male		77/124 (38.3/61.7)112/136 (45.2/54.8)	112/136 (45.2/54.8)
Institution	University	23 (11.4)	26 (10.5)
	Clinic	123 (61.2)	149 (60.1)
	Private practice	50 (24.8)	67 (27.0)
	Missing data	5 (2.5)	6 (2.4)
Position	Junior resident	27 (13.4)	33 (13.1)
	Senior resident	21 (10.4)	35 (14.1)
	Head of department	66 (32.8)	77 (31.0)
	Head of a clinic	26 (12.9)	24 (9.7)
	Self employed	48 (23.8)	65 (26.2)
	Other	13 (6.5)	14 (5.6)
		Mean (SD)	Mean (SD)
Age in years			
Female		44.69 (8.4)	44.53 (7.7)
Male		46.1 (8.4)	46.84 (7.7)
Length of experience in the psychiatric field in years		14.5 (8.4)	15.12 (8.32)
Percentage of patients diagnosed with schizophrenia or schizoaffective disorder[a]		32.3 (18.6)	31.18 (20.75)
Percentage of patients with schizophrenia or schizoaffective disorder treated with SGA		77.7 (20.9)	data not collected
Percentage of patients diagnosed with schizophrenia or schizoaffective disorder treated with depot antipsychotics		23.3 (18.4)	data not collected
Percentage of patients with schizophrenia or schizoaffective disorder ever offered a depot treatment		41.4 (23.3)	data not collected

[a] Percentage of patients diagnosed with schizophrenia or schizoaffective disorder of all patients treated by the participant.

speculatively be interpreted as clusters representing profiles of patients potentially qualifying for depot treatment. In order to reveal subgroups (clusters) of items similarly rated by the participants in sample A, the pair wise Pearson correlation coefficients were computed. To facilitate visual inspection of these correlations, they were transformed into measures of distance (by subtracting the correlation coefficient from unity) and subsequently subjected to multidimensional scaling and cluster analysis. Multidimensional scaling (MDS) seeks to represent the items as points in a low-dimensional space, in such a manner that items which have been rated similarly are displayed by points that lie close together in that space. The optimum number of dimensions is chosen based on the so-called screeplot, which shows the goodness of fit (the ability to recover the similarities of the items from the interpoint distances) as a function of the dimensionality of the space. Only when a dimension noticeably improves the fit, is it included in the MDS space. Cluster analysis represents the items in a tree-like graph (dendrogram), in which the items are the leaves; items that are connected at a low distance level in the dendogram have been rated in a similar manner.

The results in the survey of sample B were tested for statistically significant differences between the two versions (version B1 and B2) by *t*-tests for independent samples with two-sided levels of
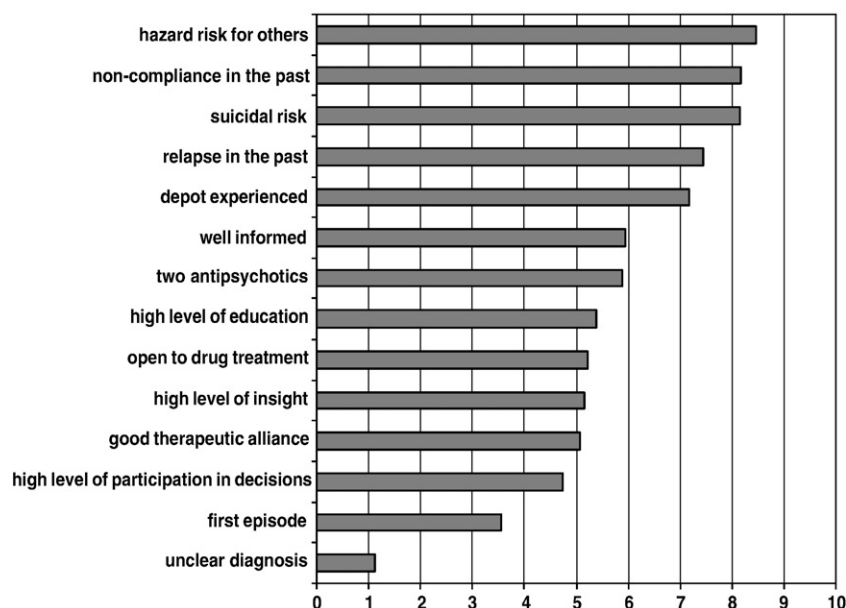

Fig. 2. Mean rating of the attributes potentially influencing the qualification for depot treatment.

significance of $\alpha = 0.05$. Data were analyzed using SPSS® Version 12.0 for Windows® and the R system for statistical computing and graphics.

3. Results

3.1. Results of sample A — patients' attributes and level of non-compliance

A total of 201 psychiatrists in sample A filled out the questionnaire. Demographic data of the participants are shown in Table 1.

3.2. Rating of patients' attributes

Almost all participants made use of the complete range of the 11-point scale, and the medians of their ratings are distributed about the numerical centre of the scale. Only fourteen participants show a rating range smaller than 6 points, and one participant scored a rating of 2 points for every attribute.

The highest scores (mean, standard deviation (SD)) representing a high level of qualification of a patient for antipsychotic depot treatment appeared with the attributes "hazard for others in the past" (8.47, SD1.9), "non-compliance in the past" (8.18, SD1.9), "suicidal threat in the past" (8.10, SD1.9), "relapse in the past" (7.44, SD2.0) and "depot experience in the past" (7.17, SD2.0) (Fig. 2).

Slightly exceeding the numerical middle of the scale (five points) were "well informed about illness" (5.94, SD2.3), "currently treated with two antipsychotics" (5.89, SD2.8), "high educational level" (5.39, SD2.4), "open to antipsychotic treatment" (5.21, SD2.6), "high level of insight" (5.16, SD2.7) and "good therapeutic alliance" (5.08, SD2.6). The attributes "high level of participation in decisions" (4.75, SD2.7), "first episode" (3.55, SD2.7) and "unclear diagnosis" (1.12, SD1.7) scored lowest.

Attributes viewed as not influencing the qualification for antipsychotic depot treatment by 10 to 20% of the participants were "high educational level" (18.4%), "depot experience in the past" (13.0%), "high level of participation in decisions" (12.9%), "currently treated with two antipsychotics" (11.5%) and "well informed about illness" (10.9%). All other attributes were considered to be of influence by more than 90% of the participants.

Table 2
Attributes of cluster I and II qualifying patients for depot treatment

Cluster I	Cluster II
Hazard for others in the past	Well informed about illness
Non-compliance in the past	High educational level
Suicidal threat in the past	Open to antipsychotic treatment
Relapse in the past	High level of insight
	Good therapeutic alliance
	High level of participation in decisions

3.3. Multidimensional scaling and cluster analysis of ratings

Included are the ratings of those 128 participants who gave a numeric rating for every item of the questionnaire. The ratings of the other 73 participants who chose the "no influence on the qualification for antipsychotic depot treatment" option on at least one of the attributes had to be excluded from this analysis because it was the goal to analyze the correlation coefficients of the complete set of attributes. Multidimensional scaling was applied to illustrate which items were scored in a similar manner. Inspection of the screeplot suggested a two-dimensional solution (Fig. 3). In this figure a closer distance between two attributes represents a higher level of correlation of the items' ratings. Items displayed in the upper left corner of the figure scored higher than items in the right corner on the bottom. Including further dimensions would not have resulted in a better fit, i.e. a more precise representation of the similarities between the attributes.

Two cluster groups of condensed attributes are visible in the two upper quadrants of the multidimensional analysis plot. Cluster I consists of four attributes: "non-compliance in the past" and "relapse in the past" in combination with "suicidal threat in the past" and "hazard for others in the past." Cluster II involves the attributes "well informed about illness," "high educational level," "open to antipsychotic treatment," "high level of insight," "good therapeutic alliance" and "high level of participation in decisions" (see Table 2). On inspection of the dendogram as it resulted from the cluster analysis (Fig. 4), the validity of the two different clusters is confirmed.
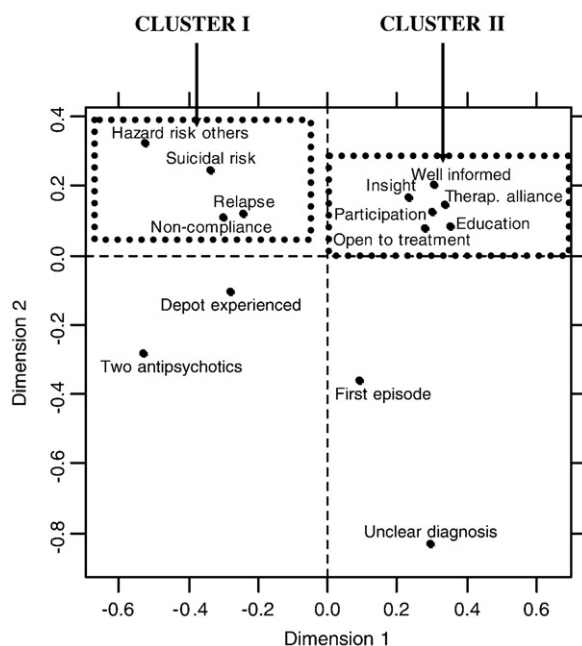

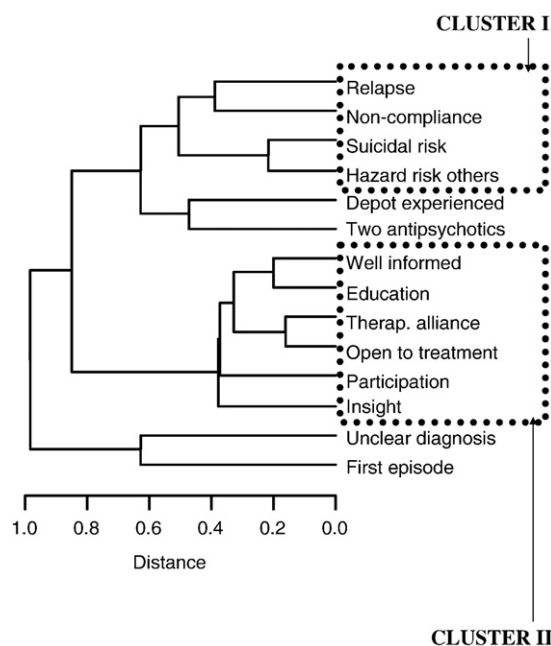Fig. 3. Multidimensional scaling analysis of correlation of ratings.

Fig. 4. Dendogram resulting from cluster analysis of correlation of ratings.

3.4. Level of non-compliance with antipsychotic treatment

Out of the 201 participants in sample A, 194 answered the question on the extent of non-compliance with antipsychotic treatment (version A1 $n=95$, A2 version $n=99$). The participants appraised the level of non-compliance in their own patients (version A1) to be 43.6% (SD24.2) while those psychiatrists asked about the non-compliance level of patients in Germany (version A2) stated 61.1% (SD18.1). The difference was statistically significant ($p<0.0001$).

3.5. Results of sample B — depot acceptance and depot proposal

Overall, the demographics of the psychiatrists in sample B were comparable to those of sample A (Table 1). Version B1 of the questionnaire was filled out by 123 participants, and version B2 by 125 psychiatrists. Participants in sample B estimated that 31.6% (SD 20.0) of their own patients and 32.6% (SD17.1) of all patients in Germany suffering from schizophrenia would accept antipsychotic depot treatment. The difference was not statistically significant. Furthermore the interviewees were asked to score on an eleven-point scale (min=0, max=10) how likely it would be for them to offer antipsychotic depot treatment to a patient either after the first or the fourth relapse. A higher rating represents a higher probability of the depot proposal. The participants rated the probability to be 6.02 (SD 2.5) for the first relapse and 8.39 (SD 1.9) after the forth relapse respectively ($p<0.0001$).

4. Discussion

The main finding of our survey is the identification of two clusters of patient attributes consistently viewed by the psychiatrists of sample A as having an influence on the qualification of patients suffering from schizophrenia for antipsychotic depot treatment. Based on their prescription practice the psychiatrists ranked a previous relapse and preceding episodes of non-compliance in the past along with the risk of suicide or a threat to others (cluster I) as the most important factors enhancing a patient's qualification for depot treatment. Another group of attributes (cluster II) includes a high level of insight, being open to antipsychotic treatment, a high educational level, a good therapeutic alliance, being well informed about the underlying illness and a high participation preference in treatment decisions was characterized with ratings slightly but consistently favoring the qualification for depot treatment. By definition the two clusters only represent attributes rated in a similar manner but these ratings are based on the prescription practice of the participants. Thus we speculatively interpret these two clusters as two different "profiles" of patients qualifying for depot treatment in the eyes of the psychiatrists in our survey.

4.1. Cluster I patient profile

The profile of patients belonging to this cluster includes recurrent relapses of schizophrenia subsequent to non-compliance as well as a high risk for self-harm or aggressive behavior, indicating a less favorable course of schizophrenia. The participants also estimated in the survey that about 40% of their own patients or respectively 60% of patients suffering from schizophrenia in general do not take their medication as prescribed, illustrating that they are aware of the non-compliance problem in the treatment of schizophrenia. Discontinuation of antipsychotic treatment or noncompliance are known risk factors for relapse (Weiden et al., 2004; Robinson et al., 1999), rehospitalizations and an overall higher potential for developing residual symptoms in the future (an der Heiden and Hafner, 2000). Depot prescription in these cases may be viewed as a way to safeguard antipsychotic treatment in order to improve a so far unfavorable course of the disease. This notion is also found in clinical studies newly initiating depot treatment in patients with schizophrenia with "noncompliance with previous treatment" being the most frequently stated reason for the switch to depot treatment (Moller et al., 2005). Furthermore the high relapse rates in patients meeting the criteria for schizophrenia and substance abuse disorders (Gupta et al., 1996) are also ameliorated by depot treatment as demonstrated in a recent study (Rubio et al., 2006).

4.2. Cluster II patient profile

The ratings of cluster II are somewhat more surprising. The comprised attributes describe a patient profile characterized by both insight in and knowledge about the underlying disease, the aim to maintain antipsychotic treatment and a well established therapeutic alliance. In all of these attributes forming cluster II, less than 20% of the participants chose "no influence on the suitability for antipsychotic depot treatment" instead of a rating of the level of influence, indicating that the attributes were considered relevant despite moderate ratings. This profile is obviously different from the cluster I patient profile. In the view of the psychiatrists, however, both types of patients qualify for a depot treatment.

4.3. Do psychiatrists have to reconsider their selection of patients for depot treatment?

The cluster I patient profile fits the current prescription stereotype for antipsychotic depot treatment (West et al., 2008, 2005). In a naturalistic, prospective study in the United States, Shi and colleagues (Shi et al., 2007) reported depot patient characteristics matching our findings to a large extent. The identification of cluster I patient profile as highly qualifying for antipsychotic depot treatment does hence reflect the current clinical practice even though depot is still reported to be underused in patients with known non-adherence (West et al., 2008, 2005).

In contrast, long-acting formulations were viewed as not to be the treatment of choice for first episode patients (FEP) in our survey, a finding that needs to be further discussed. The notion can be judged as problematic because especially FEP are at a high risk of non-compliance within the first 6 months of treatment (Kamali et al., 2006), a fact partly derived from the lower level of insight into the illness (McEvoy et al., 2006). In this patient group the strongest predictor identified for a subsequent relapse is the discontinuation of the antipsychotic medication (Robinson et al., 1999). Few studies are available on depot treatment in FEP (Tiihonen et al., 2006) but recently presented data from a study on SGA depot treatment in patients with early psychosis indicates that 72% of the study participants maintained their depot treatment for 24 months (Emsley et al., 2008), a considerably higher rate compared to oral treatment (Kamali et al., 2006; Schooler et al., 2005; Green et al., 2006). Despite the fact that up to 20% will not experience another episode (an der Heiden and Hafner, 2000) clinical guidelines do recommend antipsychotic relapse prevention for a period of at least 1 year in FEP (Lehman et al., 2004). If a psychiatrist decides to follow this recommendation depot treatment should be considered one of the options to choose from.

The fact that noncompliance with antipsychotic treatment is often underestimated has been demonstrated in several studies (Byerly et al., 2002; Remington et al., 2007) and proves even more true in regard to one's own patients, as corroborated by our findings. As a matter of fact this underestimation of noncompliance, in both one's own patients and patients in general, might influence psychiatrists, resulting in their recommending depot treatment to be seldom. This becomes even more likely in the face of the outcome of a recent study identifying "sufficient compliance with oral antipsychotic treatment" as one of the leading reasons for not prescribing depot treatment (Heres et al., 2006) among psychiatrists.

Interestingly, even the first relapse does not substantially increase the qualification of the patients for depot treatment in the participants'

eyes. After repeated relapses (namely the forth relapse in our survey) the qualification is broadly agreed on indicating that depot formulations might be considered as treatment option too late in the course of the disease. Numerous studies report a less favorable clinical outcome in the treatment response of patients after repeated relapses compared to first episode patients (Jäger et al., 2007). Taking this into account it is highly debatable whether withholding the option of depot treatment from patients with one or even no relapse can be justified.

4.4. Who qualifies for depot treatment beyond the current prescription stereotype?

The identification of patients meeting the cluster II profile as qualifying for depot treatment is of particular relevance in our opinion as this profile differs highly from the current prescription stereotype (Shi et al., 2007). It is not the number of relapses that plays a key role in these patients, but their openness to treatment and their insight into the underlying illness. These candidates do already have a better prognosis than patients with poor insight and negative approach toward antipsychotic treatment (Goldberg et al., 2001). Still they are of high interest as to whether their course of illness could be even further improved by depot treatment. So far no evidence is available indicating whether these patients may additionally benefit from depot therapy compared to oral antipsychotic treatment. Without a doubt, depot formulations will never be accepted by all patients suffering from schizophrenia as the treatment of first choice but should on the other hand not be limited in its use to cluster I patients.

4.5. Limitations of our approach

The participants attended a congress meeting and are therefore not necessarily representative of all psychiatrists in the field, so a selection bias cannot be ruled out. To our knowledge detailed information on the actual characteristics of patients open to depot treatment is not yet available in the literature, so we had to base our surveys on speculative attributes. The attributes grouped in cluster I and II have been identified in an exploratory analysis (multidimensional scaling and cluster analysis) and should be confirmed in further studies. The ratings of 73 participants had to be excluded from the multidimensional scaling and the cluster analysis due to methodological reasons. The reported results are derived from two different surveys and must therefore be interpreted independently from one another. Regarding the relationship between the number of relapses and the qualification for depot treatment we did only assess data considering a forth relapse representing multiple-relapse patients. We cannot rule out a different finding for patients with two or three previous relapses.

5. Conclusions

Patients' attributes clearly leading the psychiatrist to offer antipsychotic depot treatment are episodes of non-compliance and relapses in the past. Multiple relapses do favor the decision pro depot treatment significantly more strongly than a single relapse, whereas first episode patients are considered hardly qualifying for depot treatment. This conservative notion of depot use is supplemented by a cluster of attributes including high level of insight, openness to drug treatment, profound knowledge about the underlying disease and good therapeutic alliance, which was viewed as positively influencing the qualification for depot treatment. Patients fitting this cluster profile do also potentially qualify for depot treatment in the eyes of the surveyed psychiatrists. In contrast to this finding the current depot prescriptions rates are markedly lower than the number of potential users as indicated by the two profiles of patients qualifying for depot treatment in our survey. The reasons for this lag in depot prescription remains unclear and should be further clarified in future studies.

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