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Response prediction in treatment of patients with schizophrenia after switching from oral aripiprazole to aripiprazole once-monthly

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1. Background

Schizophrenia is a mental disorder typically starting in adolescence and young adulthood, often leading to severe impairment in patients' functioning and health- related quality of life (Kahn et al., 2015). Care for individuals with schizophrenia should comprise a wide range of psychosocial, psychotherapeutic and pharmacological treatments, offered continuously from disorder onset (Correll et al., 2018; Kahn et al., 2015). The illness course is highly heterogeneous and often associated with unfavorable outcomes affecting the lives of the patients as well as their social networks and families (Mittendorfer-Rutz et al., 2019). It is estimated that about 20 % of first-episode patients (FEP) will have a benign course leading to recovery (Altamura et al., 2007; Ram et al., 1992), however, other studies including patients with schizophrenia report high relapse rates of about 85 % within five years (Altamura et al., 2007; Carbon and Correll, 2014; Lang et al., 2013; Robinson et al., 1999).

There are no validated prognostic factors to estimate which patients will benefit from certain treatment strategies, and from psychopharmacological treatment in particular. The results of studies in biological "theragnostics" (Pene et al., 2009) have been inconclusive so far. This state of affairs is probably due in part to the syndromal approach to diagnosis of schizophrenia in DSM-5 and ICD-10, which lump diverse endophenotypes and clinical phenotypes together, and also to the

Abbreviations: AOM, aripiprazole once-monthly; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression — Severity; CGI-I, Clinical Global Impression — Improvement; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FAS, full analysis set; FEP, first-episode patient; GAF, Global Assessment of Functioning; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th edition; LAI, long-acting injectable; LOCF, last observation carried forward; SD, standard deviation; SmPC, Summary of Product Characteristics.

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heterogeneity of the overlapping symptoms and functional deficits of this multifaceted disorder (Correll et al., 2011; Hutson et al., 2017; Kahn et al., 2015). Furthermore, the analysis of the parameters used, e.g. genetic, neurochemical, neuroimaging-based, immunological or inflammatory parameters, is often too complex to be useful in clinical routine, since the measured parameters are based on methodologically heterogeneous studies and different treatments, and are thus difficult to generalize and apply to individual patients (Lai et al., 2016; Perkovic et al., 2017; Samanaite et al., 2018; Tomasik et al., 2016).

In genetics and epigenetics research, there are no comprehensive test panels to date, although there has been some notable progress in the recent years (Lisoway et al., 2021). A recent genetic-epigenetic model, which incorporated clinical information, polygenic risk score, genetic risk score, and proxy methylation level, achieved an area under curve of 0.85 in an external validation cohort (Guo et al., 2023).

Also, there are hopes that neuroimaging may reveal useful biomarkers, as it may capture phenotypic variations in molecular and cellular disease targets, or in brain circuits (Kraguljac et al., 2021). However, currently, not even performance standards for neuroimaging biomarkers (that is, acceptable sensitivity and specificity) are defined (Kraguljac et al., 2021). Machine learning algorithms that provided first imaging-driven models were able to identify first-episode drug-naïve patients with accuracies of 78.6 % and 82.5 %, respectively (Cao et al., 2020). However, reproducibility of such results is a growing concern (Ambrosen et al., 2020). When bias and overfitting are reduced, accuracies of just under 65 % are achieved (Ambrosen et al., 2020).

Poorer long-term outcomes and reduced odds for therapeutic response or remission are associated with a range of psychosocial and treatment-inherent factors found in different studies, e.g. male sex, substance use, diagnosis of schizophrenia, longer duration of psychosis, longer duration of untreated illness, earlier onset of the disorder, lack of early antipsychotic benefits, early emergence of adverse events, presence/absence of minimal improvement in psychopathology before week 4, non-adherence, greater cognitive dysfunction and poor premorbid social adjustment (Agid et al., 2003; Carbon and Correll, 2014; Chen et al., 2018; Jakubovski et al., 2015; Leucht et al., 2005a; Samara et al., 2015; Shah et al., 2020; Suvisaari et al., 2018). One very robust factor leading to reduced response and relapses is non-adherence to medication regimen (Kretchy et al., 2018; Velligan et al., 2010; Wade et al., 2017). In patients with psychotic disorders, both in first episodes and with histories of multiple psychotic episodes, nonadherence rates are high (Altamura et al., 2007; Phan, 2016) and the reasons for non-adherence are complex (Carbon and Correll, 2014; Kane et al., 2013; Lang et al., 2013; Robinson et al., 1999). In recent large cohort studies, pharmacological treatment has been shown to contribute to the prevention of relapses and hospitalizations, as well as to a reduction of mortality, paving the way for patient-related goals of appropriate role function, performance of daily routines and social interactions (Correll et al., 2016; Fountoulakis et al., 2020; Kishimoto et al., 2018). The effect of medication seems to be more pronounced when adherence is assured by use of long-acting injectables (LAIs). In real-life and long-term cohort studies, LAIs have been shown to be superior in terms of mortality and relapse rates, not only when tested against placebo but also when compared to equivalent oral medications (Taipale et al., 2018a, 2018b, 2020; Tiihonen et al., 2017, 2018).

Knowledge of prognostic factors for response to a specific medication would increase theragnostic power, help individualize and select treatments more likely to succeed and aid in avoiding time-consuming medication trials or switches. The reliable identification of easily assessable basic clinical findings as predictors of treatment response in patients with schizophrenia would be an important step towards providing more personalized treatment to the majority of patients.

Nevertheless, we still do not know which patients respond to which treatment, meaning that we are still unable to recommend a specific psychopharmacological treatment or medication regimen to patients on the basis of an array of individual predictors. All personalized medical practice requires reliable detection of characteristics that identify patients who will benefit most from targeted treatments, thereby optimizing the individual risk-benefit ratio. This kind of therapeutic personalization was proposed several years ago, but – up to now – has been introduced only in highly elaborate trials with sophisticated biological measures (Buckley and Miller, 2017; Stern et al., 2018). Such measures are hard to implement in clinical routine and are mainly done with selected trial patients, i.e. in situations that do not reflect real-world therapeutic settings. Real-world-evidence trials take a non-interventional and observational approach that bridges the gap between the controlled and selected environments of randomized controlled trials and the heterogeneous realities of a natural and uncontrolled setting with patients who are often multimorbid (Suvarna, 2018). From a statistical point of view, it should be considered that personalized recommendations are usually based on expected values, which represent a statistical average. The expected value then applies to all patients with exactly identical characteristics of the model variables. The reliability of a recommendation or prediction depends, among other aspects, on a sufficiently large data set on which the models have been developed. If only studies with a rather small number of participants are available, the prediction may be merely suitable for patient groups in which the characteristics are rather similar. Aripiprazole once-monthly (AOM) is an atypical LAI with a unique pharmacological profile. To expand knowledge of its use under routine clinical conditions, we conducted a non-interventional six-month study, in which 242 patients were treated with AOM after having been treated for an average of 9.7 months (SD: 22.3) with oral aripiprazole (Schöttle et al., 2018, 2020). In short, after oral pre-treatment, during the course of follow-up, patients improved significantly in terms of psychopathology and severity of illness, achieved better functioning and improved their well-being, with younger patients ($\leq$35 years) displaying the most pronounced benefits for these parameters.

In this paper, we aimed at identifying treatment response predictors in patients with schizophrenia treated with an assured medication supply of AOM (Schöttle et al., 2018, 2020). Based on this treatment, we used an innovative structure-detecting method known as constrained confidence partitioning (c^2p) (Fruth et al., 2022), which had been applied successfully in applications ranging from insurance to air cargo (Brieden and Gritzmann, 2012). Based on the prior literature, we hypothesized that the same method could be applied successfully in a medical context. The use of the method follows the results of a logistic regression initially performed.

2. Methods

2.1. Design

Data used for these analyses were derived from a multicenter, prospective, six-month, uncontrolled, open-label cohort study that was designed and conducted in a naturalistic setting in Germany according to the German Medicinal Product Act and approved by the Freiburg Ethics Committee international (Approval number: 014/1336; for further details see Schöttle et al., 2018). Patients $\geq$18 years old and diagnosed with schizophrenia (ICD-10) could be included in the study if the psychiatrist had chosen to switch treatment to AOM for clinical reasons according to the Summary of Product Characteristics and independently of study inclusion. All patients gave written consent (for further details see Schöttle et al., 2018). Exclusion criteria for the study were contraindications for AOM, being a member of or related to a member of the study staff, pregnancy, planning a pregnancy, breastfeeding, or expected reluctance to comply with pre-specified monitoring.

2.2. Assessments

The primary outcome parameter in the original study, where data

was sourced from, and the analysis presented here was change in psychiatric symptoms, assessed with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) from baseline to Month 3 and Month 6 (Fig. 1). The BPRS is a clinician-rated scale comprising 18 items in five domains: anxiety/depression, anergia, thought disorders, activation and hostility/mistrust (Fig. 1).

Secondary, clinician-rated endpoints included the Clinical Global Impression scale, both Severity and Improvement (CGI-S, CGI-I) (Guy, 1976) and the Global Assessment of Functioning scale (GAF) (Endicott et al., 1976).

2.3. Statistical analysis

In the present analyses, the primary outcome was a response on the BRPS, defined as at least 20 % improvement compared to baseline in the patients who were already pre-stabilized on oral aripiprazole before switching to AOM (Leucht et al., 2005b). We also considered responders in individual domains of the BPRS, defined as at least 20 % improvement compared to baseline in that specific domain.

In a first approach a classic logistic regression was performed and results can be summarized as following: In the initial regression model, those variables were included that showed a significance of maximum $p = 0.1$ with regard to the outcome in the univariate observation. These variables were weight, age at diagnosis of schizophrenia, BPRS and CGI-S-scores at baseline, housing situation, severity of disease at baseline and additional pharmacological pretreatment apart from oral aripiprazole; for detailed information on these variables see Table 1.

The least significant variable was then removed step by step until all variables had a level of $p = 0.01$ or less. The only remaining variable predicting response was BPRS-score at baseline with significance less than $p < 0.001$. However, although consisting of a highly significant variable, the model quality measured in terms of Nagelkerke's R^2 (0.164) and area under curve (0.722) was rather poor.

Nevertheless, aim of the statistical analysis was to determine significant and interpretable results that are appropriate to predict whether patients will respond to treatment with AOM.

The analytic approach, which we refer to as "constrained confidence partitioning, c^2p", consisted of three key steps very briefly described as follows; for a detailed description see (Brieden and Gritzmann, 2012; Fruth et al., 2022) and for another application see (Brieden and Gritzmann, 2020).

The first step consisted of selection of a subset of variables (Table 1) that were the most promising candidates for significantly predicting patient's response and were therefore chosen for the subsequent steps. This set of variables was chosen by D.S. and K.W. based on a literature search and clinical experience. To select the subsets for any of these variables, patients were divided into subgroups according to the values of the variables. While there was a canonical partition for ordinal and nominal variables, the partition for continuous variables was realized

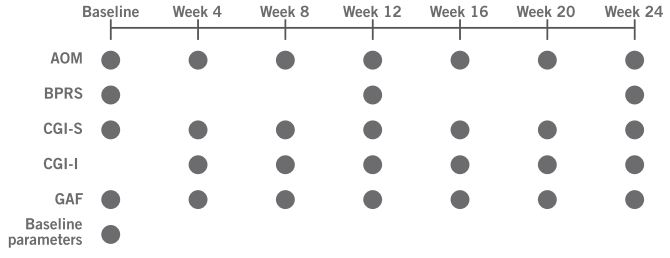

Fig. 1. Study design: assessment type and time point. Legend: patients were treated with AOM at seven points in time, each 4 weeks apart. Data for the different endpoints were collected at the indicated time points. AOM, Aripiprazole once-monthly; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression — Severity; CGI-I, Clinical Global Impression — Improvement; GAF, global assessment of functioning.

Table 1
List of variables included in the present analysis and results for the analyzed population at baseline.

	All patients (n = 217, if not indicated otherwise)	
Age	Years, mean (SD)	43.4 (14.9)
Sex	Male, n (%)	116 (53.5)
Weight	kg, mean (SD)	86.6 (21.2)
Height	cm, mean (SD)	171.8 (8.4)
Body mass index	kg/m^2, mean (SD)	29.2 (7.3)
Family status, n (%)	Single	135 (62.2)
	Married or in a relationship	50 (23.0)
	Separated, divorced or widowed	32 (14.7)
Housing situation, n (%)	Multi-person household	87 (40.1)
	One-person household	70 (32.3)
	Residential community	17 (7.8)
	Assisted living	43 (19.8)
Employment status (n = 216), n (%)	Employed	39 (18.1)
	Unemployed	66 (30.6)
	Annuitant	90 (41.7)
	Housewife/ husbandhusband	10 (4.6)
	In school/education/ re-education	11 (5.1)
Age at first episode	Year, mean (SD)	29.4 (12.6)
Age at diagnosis of schizophrenia	Year, mean (SD)	31.1 (13.0)
Number of episodes in the last 12 months before baseline (n = 215), n (%)	Mean (SD)	1.3 (1.5)
	None	39 (18.1)
	1	110 (51.2)
	2	48 (22.3)
	3	9 (4.2)
	4	3 (1.4)
	≥5	6 (2.8)
Number of episodes throughout the course of the disease (n = 216), n (%)	Mean (SD)	3.2 (1.7)
	1	17 (7.9)
	2	60 (27.8)
	3	50 (23.1)
	4	39 (18.1)
	≥5	50 (23.1)
Perception of severity of disease at baseline (n = 215), n (%)	Slightly ill	6 (2.8)
	Moderately ill	50 (23.3)
	Markedly ill	101 (47.0)
	Seriously ill	54 (25.1)
	Extremely seriously ill	4 (1.9)
Incapacity certificate caused by schizophrenia (n = 216)	n (%)	39 (18.1)
Incapacity certificate caused by schizophrenia in the last 12 months before baseline (n = 213)	n (%)	63 (29.6)

(continued on next page)

Table 1 (*continued*)

	All patients (n = 217, if not indicated otherwise)	
Hospitalization due to schizophrenia in the last 12 months before baseline	n (%)	83 (38.2)
Non-pharmacological treatment	Yes, n (%)	80 (36.9)
Non-pharmacological treatment in the last 12 months before baseline (n = 213)	Yes, n (%)	59 (27.7)
Additional pharmacological pre- treatment apart from oral aripiprazole	Yes, n (%)	125 (57.6)
Additional pharmacological treatment apart from aripiprazole once monthly (AOM)	Yes, n (%)	77 (35.5)
Current comorbidity	Yes, n (%)	94 (43.3)
Most common somatic comorbidities (multiple responses possible), n (%)	Hypertension	21 (9.7)
	Diabetes mellitus	9 (4.2)
	Obesity	11 (5.1)
	Hyperthyroidism	7 (3.2)
Most common psychiatric comorbidities (multiple responses possible), n (%)	Depression	18 (8.3)
	Anxiety	4 (1.8)
Dose of Aripiprazole once monthly (mg AOM), n (%)	400	175 (80.6)
	300	34 (15.7)
	200	7 (3.2)
	160	1 (0.5)
Brief Psychiatric Rating Scale (BPRS)	Mean (SD)	54.4 (15.6)
Clinical Global Impression of Severity (CGI-S)	Mean (SD)	4.8 (0.8)
Global Assessment of Functioning (GAF)	Mean (SD)	47.1 (13.9)

using quartiles of the parameter values. Intuitively, the greater the variance of the response rates within the respective subgroups the more suitable the single variable is to explain or to predict response, respectively. We denoted this value by inter-cluster response variance. Concerning the analysis of the full BPRS scale and any of the five subscales in each case, variables with the greatest variance were selected.

In a second step, the data were transformed to make them comparable and embeddable into a two-dimensional geometric space. Every patient was allocated within this two-dimensional space based on the two chosen variables as if these were considered solely and based on the particular response rates for each variable. For example, assuming that sex and BMI were chosen, and a male patient belonged to the first BMI quartile: in this case the response rate for males was 42 % and for patients belonging to the first BMI quartile 52 %. This patient was thus assigned to the two- dimensional point 42 %/52 %.

In the third step, using a structure-detecting algorithm for convex maximization, the data points generated in the second step were partitioned into three subgroups. In the mathematical optimization model, the partitioned data points were grouped so that points belonging to the same subgroups were grouped closely to each other and their relationship to each other could be expressed by using the square of the Euclidean norm as a distance function. Consequently, points belonging to different subgroups showed a large distance. The method used worked as an elaborated cluster technique that handled constraints, such as a minimum number of patients in each subgroup. Based on the available variables, these constraints, together with the choice of the three main clusters at the end, reliably identified homogenous patient groups responding to treatment (measured by at least 20 % reduction of the BPRS total score), with heterogeneity between the groups. We were therefore able to describe a prototypical responder depending on the results on the respective scales.

3. Results

3.1. Response — total population

Patient data from a non-interventional study (Schöttle et al., 2018) were used for the current analysis: Out of 242 patients included in the primary analysis set (Schöttle et al., 2018), 217 patients with almost complete data sets were eligible for the analyses (Table 1). Missing data had to be imputed using mean values in very few cases only.

Altogether, 127 (58.5 %) of the patients responded with improvement of their baseline BPRS total score by at least 20 % (Table 2). When the response criterion of ≥20 % was applied for improvement of the BPRS total score or of at least one BPRS domain score compared to baseline, 178 patients (82.0 %) responded.

Legend: The number of patients and rates in percent are based on the respective population analyzed (N = 217). BPRS: Brief Psychiatric Rating Scale.

Response rates differed across the BPRS domain scores (Table 2): the response rate was highest in ‘thought disorder’ as well as in ‘activation’ (n = 128 each, 59.0 %), and lowest in ‘anergia’ (n = 106, 48.9 %).

3.2. Predictors of response

3.2.1. BPRS total score

Concerning the BPRS total score, assignment of patients to a specific group and the proportion of patients responding in a specific group were mainly influenced by BPRS total score at baseline and body mass index (BMI) (Fig. 2).

Group 1 included 43 patients with an initial BPRS score above 41 and a BMI of 25 or below. In this group, the proportion of responders was 83.7 %. Group 2 included 75 patients with an initial BPRS score of above 57 and a BMI above 25. In this group, the proportion of patients responding was 70.7 %. In contrast, the proportion of responders in group 3 was 38.4 %. This group included 99 patients with both an initial BPRS score of 41 or below and any BMI quartile, as well as patients with a BPRS score between 42 and 57 and a BMI above 25.

Since BMI might reflect duration of disease, because patients with schizophrenia tend to gain weight over time, we tested whether duration of disease and BMI were correlated, finding that this was not the case (R^2 of 0.0102).

3.3. BPRS subscores

A similar pattern was seen for the BPRS domains ‘anergia’, ‘thought disorder’ and ‘activation’: assignment of patients to a specific group and the proportion of patients responding in a specific group was mainly influenced by the severity of schizophrenia measured with the BPRS and body mass index at baseline (see Supplement Figs. S1–S3).

A different pattern was seen for the BPRS domains ‘anxiety/depression’ and ‘hostility/mistrust’. Regarding ‘anxiety/depression’, the group assignment was mainly influenced by the severity of schizophrenia measured with the BPRS and number of lifetime schizophrenia episodes (Fig. 3).

The proportion of responders in group 1 was 80.7 %. This group included 93 patients with an initial BPRS score above 57 and fewer than 5 episodes. Group 2 included 30 patients with an initial BPRS score above 57, too, but with 5 episodes or more. In this group, the proportion of responders was 53.3 %. In contrast, group 3 included 94 patients with an initial BPRS score of 57 or below and any number of episodes. In this group, the proportion of responders was 37.2 %.

In the domain ‘hostility/mistrust’, group assignment was mainly influenced by the severity of schizophrenia measured with the BPRS and functionality (Global Assessment of Functioning (GAF) (Fig. 4).

Group 1 included 114 patients with a BPRS score above 57 and any GAF score. In this group, the proportion of responders was 71.9 %. Group 2 included 57 patients with an initial BPRS score of 57 or below

Table 2
Response on BPRS total score and domain scores.

	BPRS total score	BPRS domain scores				
		Anxiety/depression	Anergia	Thought disorder	Activation	Hostility/mistrust
Responders, n (%)	127 (58.5)	126 (58.1)	106 (48.9)	128 (59.0)	128 (59.0)	117 (53.9)

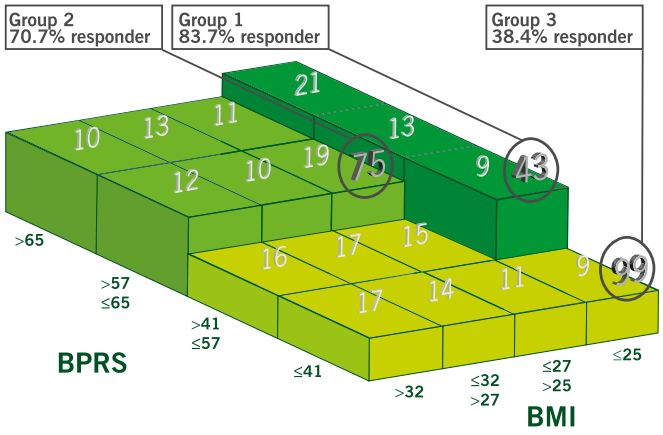

Fig. 2. Groups of patients and their response as related to the BPRS total score and BMI. Legend: The relative height of the blocks corresponds to the fraction of responders in each group. The number of patients per group is shown on top of the blocks. Groups were formed according to baseline BPRS total score and BMI. Higher BPRS scores mean greater symptom severity. In group 1 (dark green, n = 43), 83.7 % of patients responded, in group 2 (medium green, n = 75), 70.7 % of patients responded, in group 3 (light green, n = 99), 38.4 % of patients responded as measured by the BPRS total score, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

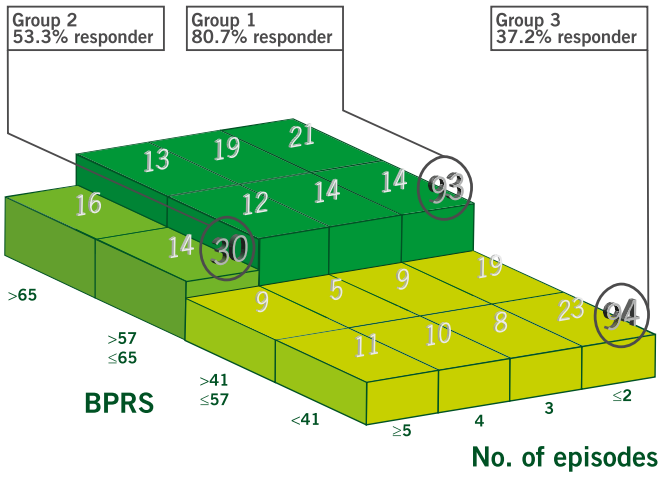

Fig. 3. Groups of patients and their response as related to BPRS anxiety/depression domain. Legend: the relative height of the blocks corresponds to the fraction of responders in the anxiety/depression domain in each group. The number of patients per group is shown on top of the blocks. Groups were formed according to the BPRS total score at baseline and the number of lifetime schizophrenia episodes. Higher BPRS scores mean greater symptom severity. In group 1 (dark green, n = 93), 80.7 % of patients responded, in group 2 (medium green, n = 30), 53.3 % of patients responded in group 3 (light green, n = 94), 37.2 % of patients responded as measured by the BPRS anxiety/depression domain, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

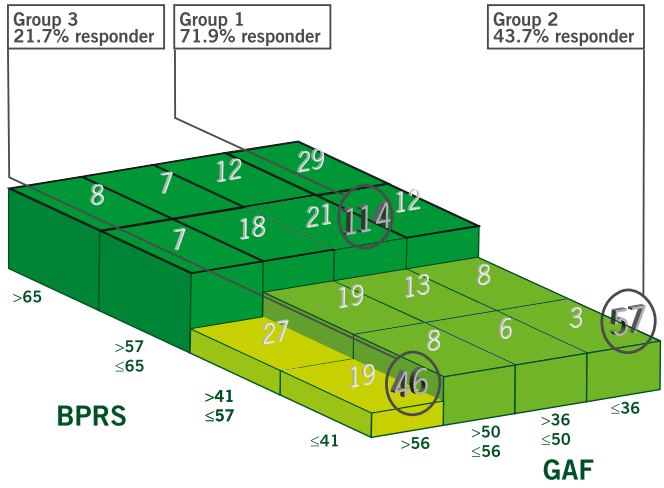

Fig. 4. Groups of patients and their response as related to BPRS hostility/mistrust domain. Legend: The relative height of the blocks corresponds to the fraction of responders in the hostility/mistrust domain in each group. The number of patients per group is shown on top of the blocks. Groups were formed according to BPRS total score and functioning (GAF) at baseline. Higher BPRS scores mean greater symptom severity, higher GAF scores mean better functioning. In group 1 (dark green, n = 114), 71.9 % of patients responded, in group 2 (medium green, n = 57), 43.9 % of patients responded, in group 3 (light green, n = 46), 21.7 % of patients responded as measured by the BPRS hostility/mistrust domain, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and an initial GAF score of 56 or below. In this group, the proportion of responders was 43.9 %. In contrast, the proportion of responders in group 3 was 21.7 %. This group included 46 patients with an initial BPRS score of 57 or below and a GAF of at least 57.

4. Discussion

In personalized medicine, markers for the prediction of response to identify those patients who will benefit from targeted treatments are highly desirable to avoid "trial and error" treatment regimes, which can be frustrating for the patient and clinician and potentially lead to non-adherence, relapse and poor long-term functional outcomes (Alvarez-Jimenez et al., 2012; Ascher-Svanum et al., 2006).

In this post-hoc analysis of a prospective non-interventional study, which was originally conducted to examine the effectiveness of AOM treatment in a naturalistic setting of usual-care patients who had been previously treated with oral aripiprazole, we used a structure-detecting approach, "constrained confidence partitioning" (c^2p) (Fruth et al., 2022), to predict response to treatment using a set of parameters used in clinical routine assessment. With this structure-detecting method, which had been used successfully in applications ranging from insurance to air cargo (Brieden and Gritzmann, 2020), we identified clinical predictors for the effectiveness of an antipsychotic medication in patients with schizophrenia after switching from oral aripiprazole to its long-acting formulation. Due to the small number of participants in the studies, predictions are only possible for homogeneous subgroups and not for individuals. In this study, two out of the 22 selected items were the main

predictors of a positive response, defined as a ≥20 % reduction in the BPRS total score. Our main findings were that a high BPRS score and a low BMI at baseline were highly predictive for a positive treatment response after switching from oral to LAI aripiprazole. Additionally, we found that BMI did not correlate with illness duration. Regarding the subdomains of the BPRS, group assignment, and thus response probability, depended not only on illness severity or body mass index, but also on number of lifetime schizophrenia episodes (less episodes predicted a higher response probability), and psychosocial functional status (worse functioning at baseline predicted a higher response probability).

An additional explorative analysis of responders (178 patients (82.0 %) improving by at least 20 % on the BPRS total score *or* at least one BPRS domain score compared to baseline) and non-responders (39 patients (18.0 %)) imply that family status and number of episodes in the 12-month before study inclusion might influence response (Supplement Fig. S4).

One has to take into account that the patients in the current study had been pre-treated with oral aripiprazole and were mostly stable at study start (Schöttle et al., 2018), although the mean CGI-S indicated moderate to marked illness severity. Nevertheless, some patients may have experienced most of their improvement before the study started, making it difficult for them to fulfill the ≥20 % improvement criterion, even though they benefitted from the treatment. The patients who benefitted most from prior treatment and were closest to remission cannot be detected by the ≥20 % criterion, leading to a floor effect in our analysis. In one study, even in first-episode patients with schizophrenia in whom the detrimental effects of long-term illness are not yet fully evident, patients improved on average by 60 % on the Positive and Negative Syndrome Scale, but up to 72 % changed or stopped medication due to inefficacy or side-effects (Kahn et al., 2008). Following a response definition of ≥20 % improvement from baseline, response rates range from 81 % in first- episode patients (Zhu et al., 2017b) to 51 % in chronic patients (Leucht et al., 2017) — however, in contrast to our study, these numbers were obtained from acutely exacerbated patient cohorts, where a higher percentage of improvement should normally be achieved (Leucht et al., 2005b). Within 1 to 1.5 years of treatment, non-adherence or discontinuation of treatment is observed in around 3 of 4 patients in both chronic and first-episode patients with schizophrenia (Kahn et al., 2008; Lieberman et al., 2005). Although these are general rates, the individual response and tolerance to antipsychotic medication is highly variable within and across patients, which makes it difficult to predict on an individual basis the respective risk-benefit ratio and the probable response to a specific treatment.

To date, no valid biomarkers or reliable patient characteristics have been found to predict whether a patient with schizophrenia will respond to antipsychotic treatment. Prognostic predictors exist for worse outcome or pharmacological response, i.e., patient-related (e.g., male sex, premorbid functional status), illness-related (e.g., duration of untreated psychosis, early negative symptoms) and medication-related factors (e.g., early non-response, pharmacogenetic variations), but these are often too weak to be of clinical importance for an individual patients or are difficult to assess in daily routine (Allen and Bishop, 2019; Fond et al., 2015; Lee et al., 2018; Suvisaari et al., 2018; Taylor et al., 2018).

In a systematic review focusing on first-episode patients, higher baseline severity of illness was, among other variables (such as shorter duration of illness and female sex) also associated with higher response rates to antipsychotic medication treatment (Zhu et al., 2017a). This result has also been observed in chronic patients, probably due to the larger leeway for symptom reduction (Furukawa et al., 2015; Rabinowitz et al., 2014; Zhu et al., 2017b). In other words, patients with schizophrenia can benefit from antipsychotic treatment throughout a spectrum of illness severity, with the most pronounced improvement from baseline in those individuals who are most severely ill. Of course, it has to be noted that symptom improvement in severely ill patients does not necessarily mean that a patient feels subjectively well or has reached the threshold for absolute symptom remission. Similarly, patients who do not reach at least a 20 % reduction in baseline symptoms may not have failed treatment if they started close to stability or remission. Moreover, the goal for long-term treatment is rather maintenance of stability than improvement from baseline, especially in patients who were initial responders, and above all in those who achieved symptomatic remission.

An explanation for our finding that low BMI scores can predict treatment response is less clear and may be only speculative. One might assume that patients with lower BMI had a shorter duration of disease, and that those less chronic patients were more amenable to improvement. Therefore, we tested whether duration of disease and BMI were correlated. Since no correlation could be detected, BMI is not an indicator of duration of disease and this hypothesis can be rejected. Contrary to our results, in a study of 126 first-episode patients treated with flupentixol decanoate, low BMI scores were found to be predictive for non-response (Chiliza et al., 2015). However, analysis of duration of illness and frequency of episodes did not support the notion that these factors were related to lower BMI. Furthermore, the comparability of flupentixol decanoate, a thioxanthene derivative with antagonistic activity mainly at D2 receptors, and aripiprazole, which is a quinolinone derivative with partial agonistic activity at D2-/D3 dopamine and serotonin 5-HT1A receptors, is limited. Due to the naturalistic study design, we were not allowed to measure blood levels of aripiprazole, therefore we cannot confirm whether higher plasma levels of the medication were achieved due to lower body weight and less body fat, possibly influencing treatment response (Jovanović et al., 2020).

Attitude towards medication also plays a role in whether patients perceive their treatment as beneficial. It is known that patients tend to attribute weight gain or being overweight to their medication (which also affects their adherence) (Wong et al., 2011). Although this is speculative, patients being pretreated with oral aripiprazole without having gained weight may have had a more positive attitude towards their treatment and therefore benefit more from treatment or get better ratings in certain BPRS items (such as hostility, uncooperativeness, etc.). Furthermore, although patients were still markedly ill at baseline, a low BMI score may be an indicator for better somatic health and therefore indicative of a lifestyle that facilitates better outcomes.

Our algorithm is an approach to predicting treatment response for patients using readily assessed clinical parameters, whereby the current study, a post hoc analysis, still has multiple limitations. The first obvious limitation is the small number of patients included in the different test samples and the focus on one medication, making it unclear to what degree our results can be extrapolated to other treatment regimes. Second, patients were pretreated with oral aripiprazole for a period during which initial improvement not measured in this study already took place and patients were already stabilized. Therefore, a floor effect limiting potential improvement in some patients could have been present. Nevertheless, the mean CGI-S score of 4.8 indicated that patients were still moderately to nearly markedly ill at baseline. Third, patients had been started clinically on aripiprazole, consented to participation and were aware they were in the study (expectation bias), which may have biased our results (selection bias). Fourth, we did not have a control group, so that the treatment effects due to medication must be described as associative rather than causal. Fifth, the initial variable selection of factors that could be entered into the model was preselected by the investigators based on a literature search and clinical experience and restricted by the information collected in the study. Sixth, no biological variables were available for inclusion in the model, but we deliberately focused on variables that would be accessible to clinicians and applicable in real-world settings. Seventh, the restriction of the final predictor variables in this study to a relatively small number of psychopathological and somatic baseline characteristics may not capture all the clinically relevant variables. For this reason, additional studies are needed. Finally, the naturalistic design of this non-interventional study makes it impossible to identify or exclude possible confounding factors.

However, despite these limitations, our findings constitute a first approach using a structure-detecting method for predictive analytics, known as "constrained confidence partitioning" (Fruth et al., 2022), to focus on clinically relevant aspects that may possibly help predict treatment response in patients with schizophrenia. In further studies, these and additional parameters should be tested in larger samples to determine their usefulness as predictors with this method, whereby results should be compared with those of other methods as well.

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Authors' contributions

WJ and KW designed the study and wrote the protocol. DS, WJ, CC, MF, HJ, AB and KW managed the literature searches and analyses. AB undertook the statistical analysis, and DS and KW wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

DS received honoraria for lectures from or has been an advisor to Janssen GmbH, ROVI, Lundbeck GmbH, Otsuka Pharma GmbH and Takeda.

KW received honoraria for lectures from or has been advisor to Janssen GmbH, Lundbeck GmbH and Otsuka Pharma GmbH.

WJ and MF are employees of Lundbeck GmbH.

CC has been a consultant and/or advisor to or has received honoraria from: Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.08.026.

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