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Identifying differential predictors for treatment response to amisulpride and olanzapine combination treatment *versus* each monotherapy in acutely ill patients with schizophrenia: Results of the COMBINE-study

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ABSTRACT

Background: Extensive research has been undertaken to predict treatment response (TR) to antipsychotics. Most studies address TR to antipsychotics in general and as monotherapy, however, it is unknown whether patients might respond favourably to a combination of antipsychotics.
Aims: This study aimed to identify differential predictors for TR to monotherapy with amisulpride or olanzapine compared to a combination of antipsychotics.
Methods: Post-hoc analysis was conducted of data collected from the COMBINE-study, a double-blind, randomized, controlled trial. Demographic and disease-related measures were gathered at baseline to predict TR after eight weeks defined by the Positive and Negative Syndrome Scale. Missing values were accounted for by a

Abbreviations: TR, treatment response.

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random replacement procedure. Attrition effects and multicollinearity were analysed and sets of logistic regression models were calculated for different treatment groups.
Results: Of the 321 randomized patients, 201 completed procedures until week eight and 197 were included in the analyses. For all treatment groups, early TR after two weeks and high subjective well-being under antipsychotics at baseline were robust predictors for TR. The propensity for early side effects also indicated a higher risk of later non-response. Specific parameter estimates were rather similar between treatment groups.
Conclusion: Early TR, drug-related subjective well-being, and early side effect propensity evolved as predictors for later TR whether to monotherapy or combination strategy. Accordingly, due to a lack of differential predictors, early and close monitoring of targeted and unwanted effects is indicated to guide respective treatment decisions.

1. Introduction

Schizophrenia is a disabling psychiatric disorder with a lifetime prevalence of approximately 1 % worldwide (McGrath et al., 2008). It is estimated that only 18–65 % of patients achieve an adequate treatment response (TR) to antipsychotic monotherapy defined as a reduction of acute symptoms by at least 20 % within the first six to twelve weeks of treatment (Leucht et al., 2009). Thus, more than one-third of patients experience only a partial response or no response at all (Lally et al., 2016; Mørup et al., 2020).

In the case of an insufficient TR, clinicians are advised to alternate between three different antipsychotic monotherapy regimens. Yet this often leads to a lengthy trial-and-error phase for patients with acutely exacerbated schizophrenia (Shimomura et al., 2021). Only after treatment with clozapine, German evidence-based treatment guidelines recommend a combination of two antipsychotics (Gaebel et al., 2020). Nevertheless, this strategy is widely adopted in clinical practice despite its questioned higher efficacy and greater risk for side effects (Baandrup, 2020; Lähteenvuo and Tiihonen, 2021). As the quest for the optimal antipsychotic medication is time-consuming (Mørup et al., 2020), the identification of predictors for TR could be paramount for clinicians, who are currently left with a trial-and-error approach of switching between treatment regimens until a sufficient TR is achieved.

Extensive research has been undertaken to identify predictors of TR, regarding both biological (Stone et al., 2009) and clinical (Carbon and Correll, 2014; Seppälä et al., 2021) predictors, with ambiguous results, especially regarding predictors for specific treatment options. Yet, most of the studies to date have either generalised different antipsychotics or focused on clozapine only despite the diverse receptor binding properties and side-effects between drugs (Asenjo-Lobos et al., 2018; Boter et al., 2009; Lambert et al., 2008). In their review, Carbon and Correll (2014) discovered that the following predictors were associated with reduced odds of TR: family history of psychosis, younger age of illness onset, lower psychopathology, greater cognitive and general dysfunction, and substance abuse. Among the predictors, early TR and adherence were repeatedly associated with increased odds for TR (Carbon and Correll, 2014). Particularly the predictor of early TR results might suggest that clinicians switch drugs to enhance symptom remission (Heres et al., 2022).

However, currently, there are no available predictors for individualized treatment decisions regarding specific antipsychotics or treatment strategies like combining substances and clinicians are reliant on their intuition (Gaebel et al., 2020). Additionally, the current recommendations for combination treatments are based on principles of "good clinical practice" due to lack of empirical evidence (Gaebel et al., 2020). Thus, differential predictors of TR to antipsychotic agents, as well as a combination of two, remain unclear. As such, empirical data is necessary.

Therefore, we aimed to determine whether (non-)response to monotherapy with either amisulpride, olanzapine, or a combination of both antipsychotics could be predicted at baseline or the very early treatment phase. We performed secondary analyses of data collected within a double-blinded, randomized controlled trial including patients with acutely exacerbated schizophrenia (COMBINE-study; Schmidt-Kraepelin et al., 2020, 2022). Various demographic, clinical, and disease-specific variables were analysed regarding their predictive validity for TR at eight weeks as indicated by the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). We hypothesised that symptoms and subjective well-being (under antipsychotics), early TR and initial compliance to medication, would predict (non-)response. To our knowledge, no study has yet investigated differential treatment predictors for poly- and mono-pharmaceutical antipsychotic TR to amisulpride and olanzapine.

2. Methods

2.1. Study design

Results of this report are based on post-hoc analyses of data from the COMBINE-study, a double-blind, prospective, and multicentre randomized controlled trial (Schmidt-Kraepelin et al., 2022). The aim was to evaluate the efficacy and safety of a combination treatment with amisulpride and olanzapine compared to either monotherapy in acutely ill schizophrenia patients in three different treatment arms. Patients with a re-exacerbation of schizophrenia or a schizoaffective disorder (ICD-10 criteria; World Health Organization, 2012) and respective acute (positive) symptoms involving an in-patient treatment were included and randomized to double-blind treatment (double-dummy design) with either monotherapy of amisulpride (200–800 mg/day) or olanzapine (5–20 mg/day) or with the combination of both (200–800 mg/day amisulpride plus 5–20 mg/day olanzapine). Targeted treatment duration was 16 weeks overall with total symptom reduction (PANSS) after eight weeks as primary outcome. A detailed description of the methods and study design was published (Schmidt-Kraepelin et al., 2020). Study approval was granted locally at study sites by ethics boards and by the German Federal Medication Agency (BfArM).

2.2. Sample

For the COMBINE-study, 13,692 patients with schizophrenia/schizoaffective disorder were screened for inclusion of whom 328 were eligible for participation and 321 cases were analysed. A CONSORT-flowchart and a detailed summary of in- and exclusion criteria can be found elsewhere (Schmidt-Kraepelin et al., 2020). Two-hundred-one patients completed procedures by week eight, with 197 included for analysis with all required data.

2.3. Procedure

The study procedures were executed according to ICH-GCP regularities following a standardised protocol and detailed schedule per study visit (Schmidt-Kraepelin et al., 2020). Clinicians screened patients for eligibility and performed a diagnostic interview, physical examination, and medical history questionnaire. Patients were allocated to one of the treatment groups in a 1:1:1 ratio. Following baseline, study visits (V) were performed every two weeks until week 16 (V8).

2.3.1. Study medication

Study medication was administered orally across groups and patients assigned to monotherapy also received a placebo (double-dummy) to ensure double-blinding of study administrators and participants. For patients receiving prior antipsychotic treatment, the previous medication and the study medication were cross-titrated. A four-level flexible dose scheme was applied in all groups starting at V0 with (1) 5 mg/day, (2) 10 mg/day, (3) 15 mg/day, (4) 20 mg/day for olanzapine and (1) 200 mg/day, (2) 400 mg/day, (3) 600 mg/day, (4) 800 mg/day for amisulpride. The same scheme (sum of each monotherapy dose-level) applied to the combination treatment arm. Treating physicians adjusted doses at their discretion based on clinical impression following the dose-level given above to reach an adequate level at V1 (Fig. A1 supplements).

2.4. Measures included in predictor analyses

2.4.1. Demographics and treatment history

Demographic characteristics, comorbidities and medical history were extracted during a clinical interview prior randomisation. Compliance with treatment was judged by the study physician in a binary format as compliant or non-compliant at each visit. Any form of previous drug abuse was categorized into one dummy variable (yes/no).

2.4.2. Symptom severity and response status

Patients' symptom severity was assessed using the PANSS (Kay et al., 1987) at each visit starting from baseline. TR was calculated according to Leucht et al. (2008) as the percentage of symptom reduction of PANSS total scores from baseline to eight weeks. Dichotomising the response status at week eight (V4) into non-responder (0- < 50 % reduction) and responder (≥ 50 % reduction) is empirically validated (Case et al., 2011; Leucht et al., 2007a, 2007b). Early TR is defined as %-reduction from total baseline scores at visit 1 (two weeks; continuous variable). Thus a more negative *i.e.* lower score represents better Early TR resulting in ORs < 1 regarding (better) later TR.

2.4.3. Disease-related variables and side effects

Disease-related characteristics and side effects under antipsychotics were assessed using the Clinical Global Impression Severity-Scale (CGI-S; Guy, 1976a) and the short form of the Subjective Well-Being Under Neuroleptics Scale (SWN-K; Naber et al., 2004). Psychotropic side effects were measured by the Dosage Record Treatment Emergent Symptom Scale (DOTES; Guy, 1976b). Further assessments included sexual functioning gauged by the Derogatis Interview for Sexual Functioning (DISF-SR; Derogatis, 1997) and extrapyramidal side effects by the Simpson Angus Scale (SAS; Simpson et al., 1970).

2.5. Data analyses

SPSS version 27 for Macintosh was used as the analysis software. The significance level was set at $p \leq .05$ (two-tailed). Missing values were replaced by normally distributed random scores with a mean/SD of the available non-missing values. The differences between variables before and after substitution of missing values were evaluated (Appendix A.1). To control for treatment selection effects, patients included in the predictor analyses ($n = 197$) were compared with those not included ($n = 124$) regarding relevant variables using independent *t*-test analysis and χ^2-test (Appendix A. 2 and A.3).

Demographic characteristics and baseline predictor variables were compared between responders (50–100 % reduction) and non-responders (0–49 % reduction) before missing values were replaced (3.1). For continuous data, mean and standard deviations were presented and groups were compared using independent *t*-tests. For detecting differences between groups in categorical variables, Chi-squared test was used. The assumption of non-multicollinearity was tested with Pearson's correlation analysis.

To identify predictors for TR and assess whether these predictors differed between treatment arms, a set of logistic regression analyses were conducted using the TR groups (responders *vs.* non-responders) as the binary dependent variable. First, an overall logistic regression model was executed for all 197 patients irrespective of treatment group. Subsequently, the corresponding analysis was performed separately for the combination and monotherapy groups (both amisulpride and olanzapine together and separately). All variables were tested univariately as predictors regarding the independent variables. In the following (multiple) analysis, the set of predictive variables were identified by stepwise (forward) selection. Total scores for PANSS and SWN-K were excluded due to multicollinearity with sub-scales. Responders (≥ 50 % reduction at V4) were set as the reference group. For categorical data, dummy variables were created, and the reference group was reported. The omnibus test of model coefficients was used to determine the overall statistical significance of the model compared to a model without independent predictor variables. Explained variance was indicated by Nagelkerke's R^2. For each predictor, Wald test for significance is provided. Odds ratios (OR) of each (univariately) significant predictor were given together with 95 % confidence intervals (CI). Percentage accuracy in classification referred to the proportion of correctly predicted cases based on the final model. Lastly, to account for potential bias resulting from the binary cut-off between responders and non-responders, multiple linear regression analyses were conducted (Appendix A.6). In this analysis, TR was quantified into a continuous change in percentages (%) from baseline to V4.

3. Results

3.1. Baseline sample characteristics

Of the 321 patients included in the COMBINE-trial (Schmidt-Kraepelin et al., 2022), 201 participated until week 8 (outcome of interest) and 197 were included in the predictor analyses. Comparison between groups revealed patients who dropped out ($N = 124$) had significantly higher symptom severity measures on PANSS positive, $t(319) = 2.02$, $p = .044$, negative, $t(319) = 2.82$, $p = .005$, and total scores, $t(319) = 2.65$, $p = .009$ (Appendices A.2 and A.3). Patients lost to follow-up were also significantly older when they showed their first psychiatric abnormality, $t(276) = 2.38$, $p = .018$ and were less likely to be compliant at V1, $\chi^2(1,321) = 10.83$, $p < .001$. Also, the proportion of general drug abuse was significantly higher in those patients dropping out, $\chi^2(1, 321) = 4.445$, $p = .035$.

Baseline comparisons between treatment responders and non-responders are depicted in Tables 1 (continuous measures) and 2 (frequencies/proportions). Table A.7 provides symptomatic development for both groups according to PANSS. Overall, 44.3 % ($n = 89$) of the patients completing V4 reached the response criterion (PANSS total reduction ≥ 50 %). The sample consisted predominantly of male patients in both groups, responders ($n = 67$, 75.3 %) and non-responders ($n = 79$, 70.5 %), were diagnosed with schizophrenia (F20, 85.4 % and 78.6 % respectively) and were on average between 40 and 42 years old. The proportion of drug groups within responders and non-responders was similar ($p = .56$; Table 2). Using *t*-test comparisons revealed that responders compared to non-responders differed significantly on four continuous SWN-K measures at baseline (see Table 1). Firstly, responders had significantly higher subjective mental functioning, $t(199) = -3.061$, $p = .003$. Secondly, responders reached higher measures of subjective physical functioning, $t(199) = -2.311$, $p = .022$. Thirdly, total SWN-K scores were overall significantly higher among responders, $t(199) = -2.98$, $p = .003$. Lastly, non-responders at V4 scored significantly higher on the DOTES scale, indicating higher psychotropic medication-related extrapyramidal side effects, $t(199) = 2.472$, $p = .014$. Regarding categorical measures (Table 2), the proportion of patients who had already received olanzapine as antipsychotic medication before study inclusion was significantly higher in the

Table 1
Baseline differences in sociodemographic and disease-related characteristics between responders ($n = 89$) and non-responders ($n = 112$) on continuous data after missing values were replaced.

Baseline characteristic	Responder		Non-responder		$t(199)$	p
	M	SD	M	SD		
Age at						
baseline	42.3	10.9	39.7	12.1	−1.592	0.11
first mental disorder	25.6	10.0	25.6	10.2	−0.616	0.54
first psychiatric treatment	28.1	9.5	27.7	11.0	−0.522	0.60
first inpatient treatment	29,4	10.6	27.5	10.4	−1.029	0.31
BMI	25.7	5.8	26.9	4.8	1.879	0.062
CGI-S	4.9	0.7	5.0	0.7	−1.592	0.11
PANSS						
positive	22.6	4.3	22.3	4.2	−0.52	0.60
negative	21.5	4.6	22.4	5.9	1.107	0.27
general	42.5	6.4	43.4	7.2	0.901	0.37
total	86.6	11.6	88.1	12.6	0.817	0.42
SWN-K						
emotional regulation	17	4.9	16.7	4.3	−1.138	0.26
self-control	17	3.4	16.2	3.5	−1.837	0.068
mental functioning	16.3	4.1	14.4	4.1	−3.061	0.003**
social integration	15.5	4.3	14.9	4.3	−1.724	0.086
physical functioning	16.6	4.3	15.1	4.7	−2.311	0.022*
total score	81.6	19.5	75.9	15.4	−2.98	0.003**
DOTES	2.9	3.6	4.2	4.2	2.472	0.014*
DISF-SR	51	33.7	53.7	35.9	−1.523	0.129***
SAS	1.1	2.3	1.3	2.2	0.776	0.44

Notes. M = mean, SD = standard deviation. PANSS = Positive and negative syndrome scale. CGI = Clinical Global Impression scale. SAS = Simpson Angus Scale. DOTES = Dosage Record Treatment Emergent Symptom Scale. DISF-SR = Derogatis Interview for Sexual Functioning. SWN-K = Subjective Well-Being Under Neuroleptics Scale short form.
* $p < .05$ indicating significance.
** $p < .01$ indicating significance.
*** $p < .001$ indicating significance.

group of non-responders, $\chi^2(1,201) = 3.951$, $p = .047$.

3.2. Logistic regression

3.2.1. Overall treatment response model

The results of the initial univariate analyses for TR predictors are depicted in Table 3a and included all patients with sufficient data ($N = 197$). Accordingly, early TR (in %; $OR = 0.95$; $p < .001$), the SWN-K subscales of mental functioning ($OR = 1.11$; $p = .002$), self-control ($OR = 1.1$; $p = .025$), and physical functioning ($OR = 1.06$; $p = .064$), side effects according to DOTES ($OR = 0.92$; $p = .025$), previous olanzapine (non-)treatment ($OR = 1.78$; $p = .052$) and sexual dysfunctions ($OR = 1.001$; $p = .08$) showed predictive properties in the univariate response prediction analyses.

To identify relevant predictors for TR a forward stepwise logistic regression model was performed. The results are summarised in Table 3b. In the final regression model, the following significant predictors of response state at V4 evolved: early TR at V1 ($OR = 0.95$; $p < .001$), SWN-K mental functioning at baseline ($OR = 1.1$; $p = .02$), and pre-randomisation olanzapine non-treatment ($OR = 2.2$; $p = .012$). The model indicated that early TR was associated with an increased likelihood for patients to be responders at V4. Additionally, higher mental functioning increased the odds for being a responder. Lastly, previous olanzapine non-treatment indicated a heightened likelihood of showing response. The resulting final logistic model was significant, $\chi^2(4) = 62.66$, $p < .001$. The model explained 36.4 % (Nagelkerke R^2) of the variance in response status.

3.2.2. Combination therapy model

To evaluate whether differential TR predictors should be considered

Table 2
Baseline differences in socio-demographic and disease-related characteristics between responders (n = 89) and non-responders (n = 112) on categorical measures after missing values were replaced.

Baseline characteristics	Responder		Non-Responder		$\chi^2(1)$	p
	n	%	n	%		
Gender					0.562	0.45
male	67	75.3	79	70.5		
female	22	24.7	33	29.5		
Treatment group					1.166	0.56
Combination therapy	34	38.2	35	31.3	0.698	0.40
Amisulpride therapy	27	30.3	40	35.7	0.430	0.51
Olanzapine therapy	28	31.5	37	33.0	0.038	0.85
Study diagnosis[c]					0.748	0.39
F20	76	85.4	88	78.6		
F25	13	14.6	21	18.8		
Independent life[a]	74	83.1	95	84.8	0.104	0.75
Partnered[a]	18	20.2	26	23.2	0.259	0.61
Employed[a, d]	28	31.5	29	26.1	0.690	0.41
Smoking[a]	73	82	85	75.9	1.108	0.29
Compliant at V1[b]	108	96.4	82	92.1	1.054	0.31
Drug abuse[a]						
General	42	47.7	52	46.4	0.033	0.86
At inclusion	22	24.7	16	14.3	3.521	0.061
Drug dependency[a]	21	23.6	26	23.2	0.004	0.95
Previous antipsychotic medication[a]						
Typical[e]	13	14.6	18	16.1	0.082	0.78
Atypical [f]	61	68.5	83	74.1	0.757	0.38
Olanzapine[g]	29	32.6	52	46.4	3.951	0.047*
Amisulpride[g]	13	14.6	8	7.1	2.953	0.086**·***
Risperidone[g]	12	13.5	20	17.9	0.709	0.40

[a] Reflects the number and proportion of subjects answering with "yes".
[b] Compliance could not be assessed at baseline and is measured at week two (V1).
[c] $N = 198$ due to missings.
[d] $N = 200$ due to missings.
[e] First generation antipsychotics.
[f] Second generation antipsychotics.
[g] Multiple answers in case of prior combination treatment possible.
* $p < .05$ indicating significance.
** $p < .01$ indicating significance.
*** $p < .001$ indicating significance.

Table 3a
Predictors with (borderline) significance in univariate analyses of logistic regression predicting likelihood for TR at V4 in overall sample ($N = 197$).

Predictor Variables	p	Odds Ratios	95 % CI for OR	
			Lower	Upper
Early TR (%)	<0.001***	0.95	0.94	0.97
SWN-K mental functioning	0.002**	1.11	1.04	1.19
SWN-K self-control	0.025*	1.10	1.01	1.20
SWN-K physical functioning	0.064	1.06	1.00	1.13
DOTES total score	0.025*	0.92	0.85	0.99
DISF-SR total score	0.080	1.01	1.00	1.02
No Previous olanzapine[a]	0.052	1.78	1.00	3.19

Notes. CI = confidence intervals. Odds ratios represent exponential B. "Early TR (%)": continuous measure of symptom reduction in percent, thus a more negative i.e. lower score represents better ER resulting in ORs < 1 regarding (better) later TR. DOTES = Dosage Record Treatment Emergent Symptom Scale. DISF-SR = Derogatis Interview for Sexual Functioning. SWN-K = Subjective Well-Being Under Neuroleptics Scale short form.
[a] Reference group to patients with prior olanzapine treatment.
* p < .05 indicating significance.
** p < .01 indicating significance.
*** p < .001 indicating significance.

Table 3b
Final model of logistic regression predicting likelihood for TR at V4 in overall sample (N = 197).

Predictor Variables	B	SE	Wald	df	p	Odds Ratios	95 % CI for OR	
							Lower	Upper
Early TR (%)	−0.05	0.01	33.15	1	<0.001***	0.95	0.94	0.97
(No) Previous olanzapine[a]	0.80	0.35	5.21	1	0.012*	2.23	1.12	4.45
SWN-K mental functioning	0.09	0.04	5.38	1	0.020*	1.10	1.02	1.19

Notes. *B* = beta value, *SE* = Standard error, *df* = degrees of freedom, CI = confidence intervals. SWN-K = Subjective Well-Being Under Neuroleptics Scale short form. Odds ratios represent exponential *B*.
[a] Reference group to patients with prior olanzapine treatment.
* $p < .05$ indicating significance.
*** $p < .001$ indicating significance.

for a combination therapy with amisulpride and olanzapine, univariate and forward stepwise logistic regression analyses were executed (n = 67). Missing values were replaced. Univariate parameters for significant variables are depicted in Table 4a. Accordingly, for combination treatment, early TR (in %; $OR = 0.94$; $p < .001$), the SWN-K subscales of mental functioning ($OR = 1.40$; $p < .001$), self-control ($OR = 1.2$; $p = .024$), social integration ($OR = 1.2$; $p = .03$), emotional regulation ($OR = 1.1$; $p = .07$), and gender ($OR = 2.5$; $p = .097$; male patients have higher probability for favorable response) indicated predictive properties in univariate analyses.

The stepwise logistic regression model parameters are listed in Table 4b. The final step four model suggested that early TR (%) at V1, mental functioning, and independent living were relevant predictors of TR. Moreover, higher symptom reduction at V1 heightened the likelihood of being responders at V4, $p < .001$. Additionally, patients having higher mental functioning at baseline had higher odds of being a responder at V4, $p = .002$. Yet, living independently decreased the odds of being responders as opposed to the reference group requiring carers, $p = .02$. However, the classification table (Appendix A.4) revealed, that this effect was based on one further patient correctly classified as a responder after inclusion of this variable in the model.

3.2.3. Overall monotherapy model

To test whether different TR predictors should be considered for amisulpride or olanzapine monotherapy, a set of stepwise logistic forward regression analyses was performed, including all patients randomized to a monotherapy (n = 130). In univariate analyses (Table 5a), the following parameters evolved as (borderline) significant: early TR (in %; $OR = 0.96$; $p < .001$), (no) prior olanzapine treatment ($OR = 2.3$; $p = .026$), and side effects as measured by DOTES ($OR = 0.92$; $p = .071$).

The parameters of the final model are specified in Table 5b and included early TR class and (no) prior olanzapine treatment as relevant predictors. The final step three logistic regression model was significant, $\chi^2(2) = 37.22$, $p < .001$, and accounted for 33.5 % of the variance (Nagelkerke R^2) in response status (Table 5b). Overall, the model designates that a reduction in early TR at week two increases the odds of patients being responders at V4, $p < .001$. Additionally, prior olanzapine treatment significantly raised the odds of being responders, $p = .015$.

Table 4a
Predictors with (borderline) significance in univariate analyses of logistic regression predicting likelihood for TR at V4 in combination treatment (n = 67).

Predictor Variables	p	Odds Ratios	95 % CI for OR	
			Lower	Upper
Early TR (%)	<0.001***	0.94	0.91	0.97
SWN-K mental functioning	<0.001***	1.40	1.18	1.66
SWN-K self-control	0.024*	1.23	1.03	1.48
SWN-K social integration	0.029*	1.19	1.02	1.39
SWN-K emotional regulation	0.070	1.12	0.99	1.26
Gender (male)	0.097	2,51	0,85	7,43
Independent living[a]	0.262	0.37	0.07	2.08

Notes. CI = confidence intervals. Odds ratios represent exponential B. "Early TR (%)": continuous measure of symptom reduction in percent, thus a more negative i.e. lower score represents better ER resulting in ORs < 1 regarding (better) later TR.
[a] Non-significant result is given additionally due to significant result in overall model; Reference group to patients answering "no" to living independently.
* p < .05 indicating significance.
*** p < .001 indicating significance.

3.2.4. Olanzapine monotherapy model

Stepwise logistic forward regression analyses were performed to identify TR predictors for olanzapine monotherapy (n = 64). According to the initial univariate analysis (Table 6a) the only significant variable was early TR (in %; $OR = 0.96$; $p < .001$).

The final model is displayed in Table 6b. The regression model was significant, $\chi^2(3) = 19.78$, $p < .001$, and explained 33.6 % of the variance (Nagelkerke R^2) in responder status at V4. Based on the analysis, increasing early TR ($p < .001$), and (higher) age at baseline was associated with higher odds of being a responder, $p = .05$. Though, patients receiving no prior amisulpride treatment had increased odds of being responders, $p = .021$.

3.2.5. Amisulpride monotherapy model

To identify differential TR predictors for amisulpride monotherapy, stepwise logistic forward regression analyses were performed (n = 66). According to the initial univariate analysis (Table 7a) different variables demonstrated (borderline) significance: early TR (in %; $OR = 0.95$; $p < .001$); DOTES side effects ($OR = 0.82$; $p = .03$); (no) prior olanzapine treatment ($OR = 3.0$; $p = .051$); SWN "self-control" ($OR = 1.16$; $p = .052$); SWN "social integration" ($OR = 1.13$; $p = .056$) and BMI ($OR = 0.88$; $p = .56$). (See Table 7b.)

The final logistic regression model for patients receiving amisulpride monotherapy was significant, $\chi^2(3) = 32.33$, $p < .001$, and explained 52.2 % (Nagelkerke R^2) of the variance between responders and non-responders. The model predicted that early favorable TR at week two ($p < .001$) and no previous olanzapine treatment increased the odds of being a responder, $p = .01$. Yet, higher DOTES scores at baseline decreased the odds of being a responder, $p = .028$.

3.2.6. Summary of the different logistic regression model results

A summary of the results from each calculated model is given in Table 8. Depicted are all (borderline) significant (univariate and multivariate) predictors. Early TR evolved as a significant predictor in all models. Likewise, different SWN-K subscales were significant predictors, with varying results across models. Additionally, side effects according to DISF or DOTES demonstrated significance, however rather specifically (DOTES for AMI) or with minor predictive power (DISF). Antipsychotic pre-treatment was another relevant predictor: non-pre-treatment with olanzapine in different models (irrespective of randomized drug group) and non-pre-treatment with amisulpride as significant (only) in the group with later (randomized) olanzapine treatment. Ultimately, certain individual predictors such as independent living, BMI, and age emerged as significant. However, their significance varied across different drug groups/models and was not consistent in both

Table 4b
Final model of logistic regression predicting likelihood for TR at V4 in patients receiving combination treatment (n = 67).

Predictor Variables	B	SE	Wald	df	p	Odds Ratios	95 % CI for OR	
							Lower	Upper
Early TR (%)	−0.07	0.02	10.20	1	0.001***	0.93	0.90	0.97
SWN-K mental functioning	0.31	0.10	9.12	1	0.003**	1.36	1.11	1.65
Independent living[a]	−2.88	1.30	4.90	1	0.027*	0.06	0.00	0.72

Note. *B* = beta value, *SE* = Standard error, *df* = degrees of freedom, CI = confidence intervals. SWN-K = Subjective Well-Being Under Neuroleptics Scale short form. Odds ratios represent exponential *B*.
[a] Reference group to patients answering "no" to living independently. SWN-K = Subjective Well-Being Under Neuroleptics Scale short form.
* $p < .05$ indicating significance.
** $p < .01$ indicating significance.
*** $p < .001$ indicating significance.

Table 5a
Predictors with (borderline) significance in univariate analyses of logistic regression predicting likelihood for TR at V4 in any monotherapy treatment (n = 130).

Predictor Variables	p	Odds Ratios	95 % CI for OR	
			Lower	Upper
Early TR (%)	<0.001***	0.96	0.94	0.97
DOTES total score	0.071	0.92	0.84	1.01
(No) Previous olanzapine[a]	0.026*	2.33	1.11	4.93

Notes. CI = confidence intervals. Odds ratios represent exponential B. "Early TR (%)": continuous measure of symptom reduction in percent, thus a more negative i.e. lower score represents better ER resulting in ORs < 1 regarding (better) later TR. DOTES = Dosage Record Treatment Emergent Symptom Scale.
[a] Reference group to patients with prior olanzapine treatment.
* p < .05 indicating significance.
*** p < .001 indicating significance.

univariate and multivariate analyses.

4. Discussion

4.1. Main results

The aim was to identify different predictors of response status eight weeks after treatment initiation in patients receiving amisulpride, olanzapine or a combination treatment for schizophrenia. Secondary analysis of a comprehensive clinical sample and data set collected as part of an RCT (Schmidt-Kraepelin et al., 2022) allowed exploratory research questions to be investigated. To our knowledge, no study has yet examined the predictors of response to combination antipsychotic treatment, particularly the combination of two potentially synergistic second-generation antipsychotic drugs, olanzapine and amisulpride.

Overall, early TR after two weeks evolved as the strongest predictor for TR after eight weeks, irrespective of treatment group. This finding corroborates that of previous research (Carbon and Correll, 2014). Another general predictor of TR was subjective well-being under antipsychotics (Naber et al., 2004). In the literature, subjective well-being has been mentioned as an outcome of functional remission, but not as a predictor of TR (Carbon and Correll, 2014; Lambert et al., 2006). As subjective well-being assessed at baseline refers to the medication status before randomisation, it may mediate the patient's expectations of any subsequent medication. In this study, vulnerability for side effects indicated a higher propensity for later non-response. This aspect could represent an interesting novelty. One possible mechanistic explanation is that prior use of antipsychotic medication leads to increased receptor upregulation, resulting in heightened sensitivity to side effects and a greater likelihood of non-response. Additionally, patients who experience higher levels of side effects may be less inclined to acknowledge symptom reduction, potentially undermining their confidence in the medication's efficacy. Even if different side effect scales are significant predictors for different drug treatment conditions, parameter estimates, especially in univariate analyses, are rather similar. In addition, some specific treatment predictor variables emerged (*e.g.* age for olanzapine monotherapy; prior antipsychotic), however as their predictive power was low, these findings should be interpreted with caution.

For patients receiving combination treatment, several predictors of TR status emerged. These included subjective well-being (which increased the likelihood of TR in the univariate analysis) and subjective mental functioning (which remained significant in the final model). As such, these findings suggest the necessity to incorporate the subjective experience of illness and treatment into routine clinical practice and to

Table 6a
Predictors with (borderline) significance in univariate analyses of logistic regression predicting likelihood for TR at V4 in olanzapine monotherapy treatment (n = 67).

Predictor Variables	p	Odds Ratios	95 % CI for OR	
			Lower	Upper
Early TR (%)	<0.001***	0.96	0.93	0.99
(No) Previous amisulpride[a]	0.448	2.46	0.24	24.97
Age at baseline	0.193	1.03	0.99	1.07

Notes. CI = confidence intervals. Odds ratios represent exponential B. "Early TR (%)": continuous measure of symptom reduction in percent, thus a more negative i.e. lower score represents better ER resulting in ORs < 1 regarding (better) later TR. Non-significant results are given due to their significance in the overall model.
[a] Reference group to patients with prior amisulpride treatment.
*** p < .001 indicating significance.

Table 5b
Final model of logistic regression predicting likelihood for TR at V4 in patients receiving any monotherapy treatment (*n* = 130).

Predictor Variables	B	SE	Wald	df	p	Odds Ratios	95 % CI for OR	
							Lower	Upper
Early TR (%)	−0.05	0.01	22.62	1	<0.001***	0.95	0.93	0.97
(No) Previous olanzapine[a]	1.08	0.44	5.97	1	0.015*	2.94	1.24	6.98

Note. *B* = beta value, *SE* = Standard error, *df* = degrees of freedom, CI = confidence intervals. Odds ratios represent exponential *B*. [a]Reference group to patients with prior olanzapine treatment.
* $p < .05$ indicating significance.
*** $p < .001$ indicating significance.

Table 6b
Final model of logistic regression predicting likelihood for TR at V4 in patients receiving olanzapine treatment ($n = 64$).

Predictor Variables	B	SE	Wald	df	p	Odds Ratios	95 % CI for OR	
							Lower	Upper
Early TR (%)	−0.06	0.02	11.39	1	<0.001***	0.94	0.90	0.97
(No) Previous amisulpride[a]	−3.34	1.45	5.31	1	0.021*	28.08	1.65	479.08
Age at baseline	0.06	0.03	3.64	1	0.05*	1.06	1	1.12

Note. *B* = beta value, *SE* = Standard error, *df* = degrees of freedom, CI = confidence intervals. Odds ratios represent exponential *B*.
[a] Reference group to patients with prior amisulpride treatment.
* p < .05 indicating significance.
*** p < .001 indicating significance.

Table 7a
Predictors with (borderline) significance in univariate analyses of logistic regression predicting likelihood for TR at V4 in amisulpride monotherapy treatment (n = 67).

Predictor Variables	p	Odds Ratios	95 % CI for OR	
			Lower	Upper
Early TR (%)	<0.001***	0.95	0.93	0.98
SWN-K self-control	0.052	1.16	1.00	1.35
SWN-K social intergration	0.056	1.13	1.00	1.29
DOTES total score	0.029*	0.82	0.68	0.98
(No) Previous olanzapine[a]	0.051	3.00	0.99	9.05
BMI	0.056	0.88	0.77	1.00

Notes. CI = confidence intervals. Odds ratios represent exponential B. "Early TR (%)": continuous measure of symptom reduction in percent, thus a more negative i.e. lower score represents better ER resulting in ORs < 1 regarding (better) later TR. SWN-K = Subjective Well-Being Under Neuroleptics Scale short form. DOTES = Dosage Record Treatment Emergent Symptom Scale.
[a] Reference group to patients with prior olanzapine treatment.
* p < .05 indicating significance.
*** p < .001 indicating significance.

provide psychological interventions to improve well-being alongside antipsychotic treatment, particularly in acutely ill patients receiving combination therapy. In addition, independent living status proved relevant in the final model. However, the classification table showed that only one additional case could be correctly identified based on the input of patients' living status into the model, possibly due to chance rather than clinical relevance.

For monotherapy in general and amisulpride treatment, prior use of olanzapine decreased the likelihood of reaching responder status at week eight among patients in the two monotherapy groups. This could be due to the extensive receptor binding profile of olanzapine, which is one of the broadest in the class of antipsychotics (Siafis et al., 2018). In addition, the cross-titration phase of one week might be rather brief especially for olanzapine (Stahl, 2021) leading to less favorable treatment outcomes (Cerovecki et al., 2013). A detailed analysis of the specific response rates for the (randomized) treatment groups according to prior olanzapine treatment or not (Table A.5 supplements) provides a more perspicuous picture. Whereas in the case of no prior olanzapine treatment, the response was somewhat more favorable in all treatment conditions (all greater equal 50 % compared to 45 % overall). Furthermore, in the case of prior olanzapine treatment, the response was comparably high (48.3 %) only under combination treatment, which was noticeably lower in both monotherapies (25 % or 35 % respectively). It appears that changing to another monotherapy after olanzapine treatment is less effective than initiating a combination treatment. A similar pattern emerges regarding prior amisulpride treatment (or not). Likewise, findings from the OPTiMiSE-study in first-episode patients suggest that switching from amisulpride to another monotherapeutic (olanzapine) treatment did not result in higher remission rates (Kahn et al., 2018) whereas Heres et al. (2022) found somewhat higher remission rates after a change of antipsychotics (among amisulpride and olanzapine) in case of prior insufficient TR. In our study, after both situations, whether people had prior amisulpride or not, combination treatment resulted in higher TR rates compared to any further monotherapy. Additionally, different predictors of TR emerged for amisulpride. Particularly, psychotropic side effects at baseline reduced the likelihood of achieving TR with amisulpride monotherapy.

4.2. Strengths and limitations

Several limitations should be considered. First, dropout rates are comparatively higher in this study (Kishi et al., 2020). Yet, the inclusion criteria of this study aimed to specifically represent severely ill patients with schizophrenia, so a greater dropout rate was to be expected (Schmidt-Kraepelin et al., 2022). Secondly, despite the large set of predictors, it is likely that other measures may also be clinically meaningful. This is true, for example, of the duration of untreated psychosis, which has been shown to be a highly relevant predictor of TR and remission (Carbon and Correll, 2014; Crespo-Facorro et al., 2007). Likewise, compliance was assessed as binary measure restricting a more differentiated analysis and might have contribute to non-significant predictive results contrary to former findings. Additionally, although the cut-off has been previously validated and is considered more practical for clinical application (Leucht et al., 2007a, b, 2008), the dichotomisation of the outcome may lead to information loss. Nevertheless, regression analyses regarding TR as continuous measure led to comparable results (Table A.6 supplements; additional data available on

Table 7b
Final model of logistic regression predicting likelihood for TR at V4 in patients receiving amisulpride monotherapy ($n = 66$).

Predictor Variables	B	SE	Wald	df	p	Odds Ratios	95 % CI for OR	
							Lower	Upper
Early TR (%)	−0.09	0.02	13.69	1	<0.001***	0.91	0.87	0.96
(No) Previous olanzapine[a]	2.40	0.94	6.52	1	0.01*	11.02	1.75	69.47
DOTES	−0.38	0.16	5.88	1	0.02*	0.68	0.50	0.93

Note. *B* = beta value, *SE* = Standard error, *df* = degrees of freedom, CI = confidence intervals. Odds ratios represent exponential *B*. DOTES = Dosage Record Treatment Emergent Symptom Scale.
[a] Reference group to patients with prior olanzapine treatment.
* p < .05 indicating significance.
*** p < .001 indicating significance.

Table 8
Summary of all predicting variables for TR by model.

Predictor Variable	Model				
	Overall Treatment	Combination treatment	Monotherapy treatment	Amisulpride treatment	Olanzapine treatment
Early TR (%)	u m	u m	u m	u m	u m
SWN-K mental functioning	u m	u m			
SWN-K self-control	u	u		(u)	
SWN-K physical functioning	(u)				
SWN-K social integration		u		(u)	
SWN-K emotional regulation		(u)			
DOTES	u		(u)	u m	
DISF-SR	(u)				
(No) Previous olanzapine	(u) m		u m	(u) m	
(No) Previous amisulpride					m
Independent living[a]		(u) m			
BMI				(u)	
Age at baseline					m

Note. u = univariate (only), m = multivariate (only), u m = univariate and multivariate. '()'/brackets indicate borderline significance ($0.05 < p < .1$). DOTES = Dosage Record Treatment Emergent Symptom Scale. DISF-SR = Derogatis Interview for Sexual Functioning. SWN-K = Subjective Well-Being Under Neuroleptics Scale short form.

[a] Reference group to patients answering "no" to living independently.

request). Likewise, sensitivity analyses including other cut-off scores for definition of the dichotomous response outcome categories (30 % as compared to the used 50 % score) or only the PANSS-positive symptom domain (as compared to the used PANSS-total score) revealed highly comparable results (early response/ER as the strongest predictor, additional predictor SWN-K 'mental functioning' or overall symptom severity at baseline as indicated by CGI). Results are listed in the supplements (see Tables A.8/9/10). In addition, high rates of pre-treatment with olanzapine or amisulpride might be a source of bias regarding group differences in response rates and evolving predictors among treatment groups. Furthermore, the sample size was small and as such the results might have increased alpha error in general and especially regarding the results of significant effects of antipsychotic pre-treatment given the low cell frequencies. Lastly, the sample consisted mostly of white, male Caucasian patients limiting the generalisability to patients of other ethnicities and genders.

4.3. Conclusion

The most powerful predictors for TR, even for antipsychotic combination treatment, included early response, subjective well-being under antipsychotics and propensity for side effects. Thus, tight monitoring of side effects is recommended and may potentially justify an early treatment regime change. While we aim to avoid over-interpretation of study results, it suggests that insufficient efficacy in monotherapy with a highly effective antipsychotic, particularly amisulpride or olanzapine, may predict a more favorable response to combination treatment with both amisulpride and olanzapine.

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CRediT authorship contribution statement

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Appendix A. Supplementary data

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