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# Response trajectories in "real-world" naturalistically treated schizophrenia patients

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ABSTRACT

*Background:* To date, research has identified distinct antipsychotic response trajectories yet focussing on data from randomized-controlled trials (RCTs). Therefore, the heterogeneity of response in "real-world" schizophrenia patients is still unknown.
*Methods:* Antipsychotic response was evaluated in 399 patients suffering from a schizophrenia spectrum disorder within a naturalistic multicenter study of the Competence Network on Schizophrenia using latent class regression. Baseline and illness-related variables were compared between the different trajectory classes as well as currently proposed outcome definitions (early improvement, response, remission) using univariate tests. In order to predict the trajectory group membership classification and regression tree analysis were furthermore performed.
*Results:* Five distinct trajectories of antipsychotic response were identified: Class 1 (15%) showing an early and considerable improvement, Class 2 (14%) incorporating patients with the greatest response to treatment, Class 3 (34%) again showing an early improvement to treatment yet with a slightly lower degree of improvement, Class 4 (22%) featuring patients gradually responding to treatment, and Class 5 (15%) with the poorest antipsychotic response. Fewer depressive symptoms at admission, better functioning, a shorter duration of illness and less previous hospitalizations were found to be significant predictors of good response. No considerable differences were found comparing the present results to the previous trajectory analyses deriving from RCTs.
*Conclusion:* Our results underline the heterogeneous course of response independent of the study or treatment design suggesting that the diversity in schizophrenia response and outcome is determined primarily by different pathophysiological underpinnings.



## 1. Introduction

In modern psychiatry, schizophrenia is believed to be a severe and heterogeneous disorder resulting in a favorable outcome in some patients although others may suffer from a deteriorating course of the illness (Wiersma et al., 1998). Since the introduction of antipsychotic treatment clinicians and researchers have tried to understand

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patterns of treatment response in schizophrenia and to identify and support patients in danger of a poor response in order to adopt specific treatment adaptations improving course and outcome of the illness (Gaebel, 1996). However, despite significant research in this field factors determining response to antipsychotic treatment are still not fully understood with inconclusive and contradictory results (Correll et al., 2003). But, understanding the characteristics of patients not responding well to treatment would be the first step to find better treatment strategies for them.

To identify patients responding well or poorly to antipsychotic treatment, traditionally predefined thresholds are applied to categorize patients into responders on one side and non-responders on the other (Stauffer et al., 2011). This dichotomizing approach however bears numerous problems. Often the applied cut-offs are arbitrarily chosen and dichotomizing a continuous score was found to lead to inefficient analyses (Uher et al., 2010).

Therefore, in order to shed light on actions of antipsychotic response in schizophrenia a new statistical method has been introduced lately to quantify the extent of heterogeneity in trajectories of response using so called mixed mode latent regression modeling. This approach bears the advantage of categorizing patients based on temporal patterns of change searching for heterogeneity as it naturally occurs in clinical data (Muthen et al., 2002). Levine and Leucht were among the first to perform growth mixture modeling in schizophrenia patients and reported five distinct treatment response trajectories characterized by varied amelioration levels (Levine and Leucht, 2010). Three trajectory classes showed a treatment response trend of amelioration, one class only a small reduction on the Brief Psychotic Rating Scale and one class featured a considerable symptom reduction during the first two weeks (Levine and Leucht, 2010). Also, Case et al. calculated response trajectories finding four distinct response trajectories in contrast to Levine and Leucht, however, identifying very similar response patterns with most patients achieving a moderate improvement with rapid symptom improvement in 12.5% of the patients and 2.3% with unsustained improvement (Case et al., 2010). The authors suggested that the observed heterogeneity might represent specific endophenotypes of response with different etiologic underpinnings (Case et al., 2010).

In the meanwhile, several authors calculated treatment response trajectories in schizophrenia patients, however, all previously published articles focus solely on data deriving from randomized controlled trials examining different atypical antipsychotics (Levine and Rabinowitz, 2010; Marques et al., 2010; Levine et al., 2011; Stauffer et al., 2011). This limits the clinically relevant implications concurrently leaving out results of treatment with typical compounds or combination treatments. Besides, in terms of predicting the trajectory group membership only few variables have been examined so far regarding their predictive validity (Levine and Rabinowitz, 2010). Also, it is unclear how far the response trajectories overlap with currently established response and outcome definitions which might help to evaluate their clinical adequacy and use. Therefore, to expand prior research, we wanted to perform growth mixture modeling in schizophrenia patients treated within a naturalistic trial analyzing a variety of sociodemographic and clinical variables in terms of their value to predict the patient's response trajectory class.

## 2. Methods

### 2.1. Subjects

Data were collected at eleven psychiatric university hospitals and three psychiatric district hospitals within a multicenter follow-up program by the German Research Network on Schizophrenia (Wolwer et al., 2003). All patients admitted to one of the above mentioned hospitals between January 2001 and December 2004 with a diagnosis of schizophrenia, schizophreniform disorder, delusional disorder and schizoaffective disorder according to DSM-IV criteria were selected for inclusion. Subjects were aged between 18 and 65 years. Exclusion criteria were the presence of a head injury, a history of major medical illness and alcohol or drug dependency. An informed written consent had to be provided to participate in the study. The study protocol was approved by the local ethics committees (Jager et al., 2007).

### 2.2. Assessments

DSM-IV diagnoses were established by clinical researchers on the basis of the German version of the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). Sociodemographic and course-related variables were collected using a standardized documentation system (Cording, 1998). To assess symptom severity and the level of antipsychotic response the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1988) was applied. To compare the patients within the different response trajectories further rating scales were used. The 17-item version of the Hamilton Depression Rating Scale (Hamilton, 1960) and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987) were applied to evaluate the level of depressive symptoms and adverse events, respectively. The patient's functioning was examined via the Global Assessment of Functioning Scale (GAF) (American Psychiatric Association, 1994) and the Social Occupational Functioning Scale (SOFAS) (American Psychiatric Association, 1994). To evaluate the patients' premorbid adjustment the short-scale for premorbid social-personal adjustment of the Phillips Scale was applied (Phillips, 1953). Ratings were assessed by trained clinicians at baseline and subsequently every two weeks until discharge. All raters had been trained using the applied scales. A high inter-rater reliability was achieved (ANOVA-ICC > 0.8 based on the PANSS). In order to establish and maintain the high inter-rater reliability interactive video-based rater-training sessions were regularly performed throughout the study period in every participating hospital. To further assure an accurate and consistent documentation the collected data were sent to the study center on a regular basis to be checked for completeness and coherence. Rater seminars between the centers were held before the study began.

### 2.3. Statistical analysis

In a first step, different courses of treatment response were identified using latent class regression, also known as latent class growth analysis (LCGA). To model the course of treatment response, 49 different parameterizations with orthogonal polynomials (1–7°), semi-parametric B-splines (1–7°, 2–9 df), or natural cubic splines (3–9 df) were investigated. Trading off between goodness-of-fit and complexity, the model minimizing the Bayesian Information Criterion (BIC) was chosen. Models were estimated by the classification–expectation–maximization (CEM) algorithm. However, in order to obtain regular maximum likelihood estimates, the selected model was finally re-estimated by the original CEM algorithm using the maximum a posteriori (MAP) classification of the best CEM fit as initial configuration. The identified clusters resulting from the MAP classification were numbered according to the percentage reduction in the PANSS total score in each class.

In a second step, the identified subgroups of patients were compared on various clinical and baseline characteristics using Fisher's exact test for categorical variables, and the Kruskal–Wallis test or the ANOVA F-test for metric variables, depending on the assumption of normality. The selection of these clinical and baseline characteristics goes back to previous publications of response trajectories deriving from randomized controlled trials in order to compare whether there would be a difference in the potential influencing variables