Antipsychotic Response in the First Week Predicts Later Efficacy

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Abstract

Background and Aims: Time of onset of antipsychotic action is still a debated matter. We aimed to replicate and extend previous findings that early response can predict subsequent non-response. *Methods:* 86 acutely psychotic patients treated with haloperidol were studied. *Results:* A PANSS reduction ≤16% at 1 week predicts non-response at 3 weeks of treatment (specificity 92%, sensitivity 82%). Conversely, a PANSS reduction ≥23% at 1 week of treatment predicts response at 3 weeks, with a specificity of 84% and a sensitivity of 86%. *Conclusion:* Our results confirm that an early response to antipsychotic treatment accurately predicts the treatment effectiveness and extends it to a prediction performed as early as 1 week.

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Introduction

Since their introduction about half a century ago, antipsychotics constituted the mainstay of pharmacologic treatment of schizophrenia. For years, it has been stated in textbooks and guidelines that the onset of antipsychotic action is delayed and that it takes 8 weeks or more before the onset of therapeutic benefits is produced [1]. However, in the last years a growing body of evidence has shown that a substantial amount of improvement occurs within 2 weeks or less of initiating antipsychotic treatment, with effects seen in some patients as early as 24 h [1, 2]. Failure to respond within this time frame has been shown to strongly predict later non-response in several studies [3–7]. These studies applied various symptom improvement thresholds to define early response, including the absolute lack of improvement (0% reduction of BPRS score), a 10% symptom reduction, as well as 20% symptom improvement on the BPRS or PANSS. Also the time point at which early response was assessed in previous studies was different, but most of them focused on the response after 2 weeks of treatment. Despite such methodological differences, overall these studies demonstrated that early non-response to antipsychotic treatment is

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a robust predictor of subsequent lack of response in patients with schizophrenia. These findings have important implications for the treatment of patients with schizophrenia: they may allow to avoid ineffective treatments and the side effects related to them, to ensure an adequate trial in subjects who are likely to benefit, to early identify subjects who may benefit from a different antipsychotic agent and, therefore, to reduce the long-term clinical, functional, and economic harm associated with inadequate treatment [8]. Taking into account the high clinical relevance that early prediction of response may represent, we aimed to replicate the previous finding that early response can predict subsequent non-response at endpoint in a sample of acutely ill patients treated with haloperidol. We focused on the response after 1 week of treatment in order to verify if also at this point it may represent a robust predictor of the final outcome. More in details, the aims of the present study were: (1) to evaluate whether early response (defined as the percentage reduction of PANSS total score at 1 week of treatment, adjusted for the minimum score of the scale) can predict the outcome at the endpoint (defined according to the adjusted percentage reduction of PANSS total score at 3 weeks of treatment), and (2) to identify the optimal early response threshold that best predicts subsequent resistance at 3 weeks of treatment.

Materials and Methods

Patients

Data for this study were drawn from a 4-week naturalistic study of haloperidol in psychotic patients [for details, see 9]. In brief, acutely psychotic inpatients for this study were enrolled when admitted at the Department of Psychiatry, Ludwig Maximilians University of Munich, Germany. Inclusion criteria were: age from 18 to 60 and a diagnosis of schizophrenia confirmed by two psychiatrists by administration of the Structured Clinical Interview for DSM-III-R axis I disorders (SCID-I) interview. Exclusion criteria were a known contraindication for treatment with haloperidol, tardive dyskinesia, severe neurological or medical disorders, organic brain diseases, pregnancy and acute suicidality. Furthermore, at baseline, patients were excluded if they received co-medication, such as β-blockers, antidepressants, biperiden or benzodiazepines with a possible influence on the antipsychotic treatment and its side effect. Patients were treated with haloperidol without any dose limitation during the acute phase of the illness. After this phase, they were switched to a second-generation antipsychotic either if they developed motor side effects or for maintenance after the control of positive symptoms was reached. Only data deriving from the first phase of the study were used for the purposes of the present work. Patients were assessed for their socio-demographic and clinical variables at baseline, and symptoms severity was assessed using the PANSS

scale at baseline and days 1, 7, 14, 21, and 28 [10]. Haloperidol-induced side effects were assessed through the following tests: Extrapyramidal Symptom Rating Scale (ESRS) [11], Udvalg for Kliniske Undersøgelser side effects rating scale (UKU) [12], and the Barnes Akathisia Scale (BAS) [13]. All the scales were administered by two senior psychiatrists; inter-rater evaluation gave reliable results (κ > 0.80). The study was approved by the local ethics committee and carried out in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained at the recruitment for each patient included.

Statistical Analysis

In order to examine the ability of early improvement to predict patients' response status at endpoint, receiver-operating characteristics (ROC) curves with area under the curve (AUC) values were calculated. The ROC curve is a graphical plot of sensitivity versus (1-specificity) and the AUC represents a measure of the overall discriminative power: a value of 0.5 for the AUC indicates no discriminative ability, while a value of 1.0 indicates a perfect power [14]. The percentage PANSS reduction at 1 week was used as a predictor and it was calculated using the formula $P\% = [(P0 - P1)/P0] \times 100$, where $P0$ was PANSS score at baseline and $P1$ was PANSS score at 1 week of treatment [15–17]. According to the suggestions by Obermeier et al. [15, 17] and Leucht et al. [16], PANSS scores were corrected by subtracting 30 points (the minimum value of PANSS scale) to every PANSS score before calculating percent changes. Subsequent response was calculated at 3 weeks of treatment instead of 4 due to the high number of subjects exiting the study (56 patients) at the fourth week of the study and it was defined as follows: (1) poor response: <26% reduction in adjusted PANSS score at 3 weeks of treatment [18] and (2) good response: >51% reduction in adjusted PANSS score at 3 weeks of treatment [18].

We also searched for the cut-off (early response threshold) that represents an optimum trade-off between sensibility and specificity by identifying the point of the curve with the maximum Youden index. The Youden index is an indicator for the balance between sensitivity and specificity and its formula is: Youden index = sensitivity (%) + specificity (%) – 1, the optimum value being +1 [19]. Data were analyzed with R software version 2.12.1.

Results

A total of 101 subjects were enrolled in the study; among them, 15 dropped out before the third week of the study (all of them experienced intolerable side effects) and were therefore excluded from the analysis. The final sample was therefore constituted by 86 subjects. Clinical and demographic characteristics of the sample are reported in table 1. The results of the ROC analysis are summarized in table 2. ROC curves are reported in figure 1 (early response as a predictor of poor response at 3 weeks) and figure 2 (early response as a predictor of good response at 3 weeks). Early response (i.e. the percentage

Table 1. Clinical and demographic characteristics of the sample (mean ± SD)

Variable	Results
Age, years	35 ± 11.6
Sex	Male = 48 (56%), female = 38 (44%)
Age at onset, years	29.3 ± 9.8
Disease duration, years	5.6 ± 8.1
PANSS score at baseline	104 ± 18
Number of episodes	2.8 ± 3.2
Number of hospitalizations	2.7 ± 2.7
Previous antipsychotic medication	Yes = 69 (80.2%), no = 17 (19.7%)
Haloperidol dosage day 7, mg/day	11.36 ± 5.88
Haloperidol dosage day 21, mg/day	10.9 ± 6.5
Diagnosis	Schizophrenia, paranoid type = 44 (51.1%)
	Schizophrenia, undifferentiated type = 4 (4.6%)
	Schizophrenia, catatonic type = 4 (4.6%)
	Schizophrenia, disorganized type = 3 (3.4%)
	Schizoaffective disorder = 17 (19.7%)
	Brief psychotic disorder = 8 (9.3%)
	Delusional disorder = 2 (2.3%)
	Schizophreniform disorder = 4 (4.6%)

PANSS reduction at 1 week of treatment) showed to be a good predictor of subsequent response at 3 weeks of treatment: AUC was >0.9 both for poor improvement and for good improvement, indicating an excellent discriminative ability. The cut-off with the best trade-off between sensibility and specificity as assessed with the Youden index was 16% for patients showing a poor response. Thus, a PANSS reduction ≤16% at 1 week predicts a less than 26% PANSS reduction ('poor response') at 3 weeks of treatment, with good values of specificity (92%), sensitivity (82%), positive predictive value (85%) and negative predictive value (78%). The best threshold for the prediction of a good response according to Youden index was 23%, which means that a PANSS reduction ≥23% at 1 week of treatment predicts a good response (i.e. a PANSS reduction ≥51%) at 3 weeks, with a specificity of 84%, a sensitivity of 86%, a positive predictive value of 75% and a negative predictive value of 88%. Overall these data suggest that when a patient does not achieve a symptom reduction of at least 16% within the first week of treatment, it is likely that at 3 weeks of treatment it will display a resistance to current treatment (i.e. a symptom reduction ≤26%). Further, when a symptom reduction ≥23% is obtained within the first week of treatment, it is possible to predict a good response (a symptom reduction ≥51%) at 3 weeks of treatment.

Table 2. Prediction of response at 3 weeks by percentage PANSS reduction at 1 week

Outcome	AUC	Threshold, %[1]	Sensitivity, %	Specificity, %	PPV %[2]	NPV %[3]
Poor response	0.923	16	82	92	85	78
Good response	0.915	23	86	84	75	88

[1] Percentage PANSS reduction at 1 week with the best trade-off between sensitivity and specificity according to Youden index.
[2] Positive predictive value.
[3] Negative predictive value.

Discussion

The present study was carried out to evaluate whether early response to antipsychotic drug treatment (i.e. percentage symptom reduction at 1 week of treatment, adjusted for the minimum score of PANSS scale) can predict subsequent response at endpoint, defined according to the adjusted PANSS total score percentage reduction at 3 weeks of treatment. We also investigated the optimal early response threshold that best predicts subsequent resistance at 3 weeks of treatment.

Although for decades it has been stated in textbooks and guidelines that the onset of antipsychotic action is delayed, recent research has showed that it can occur rap-
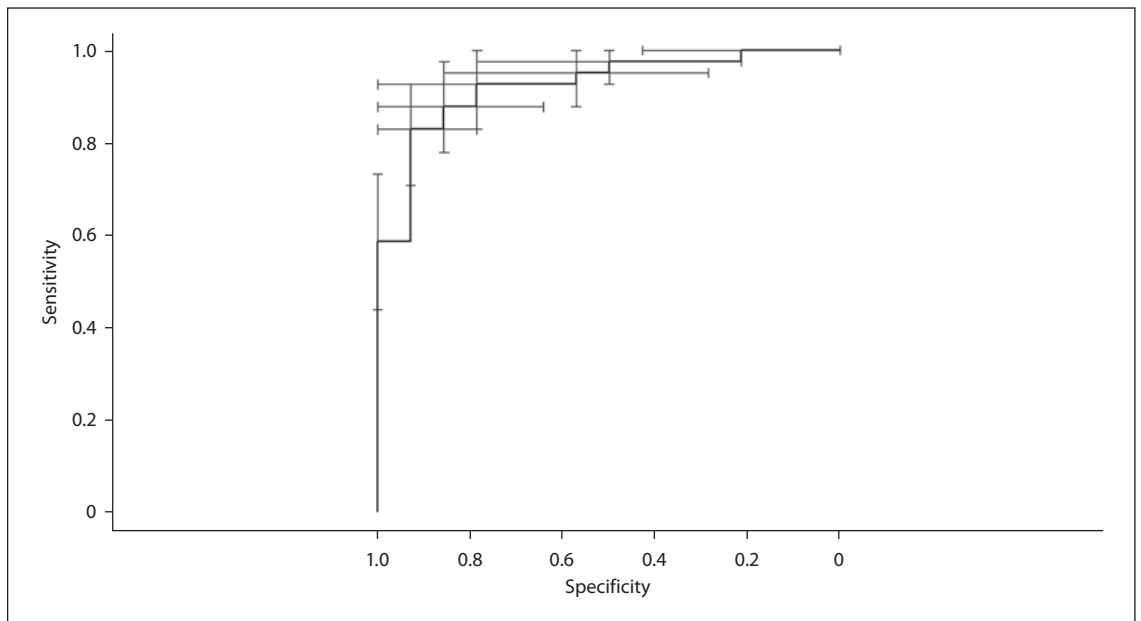
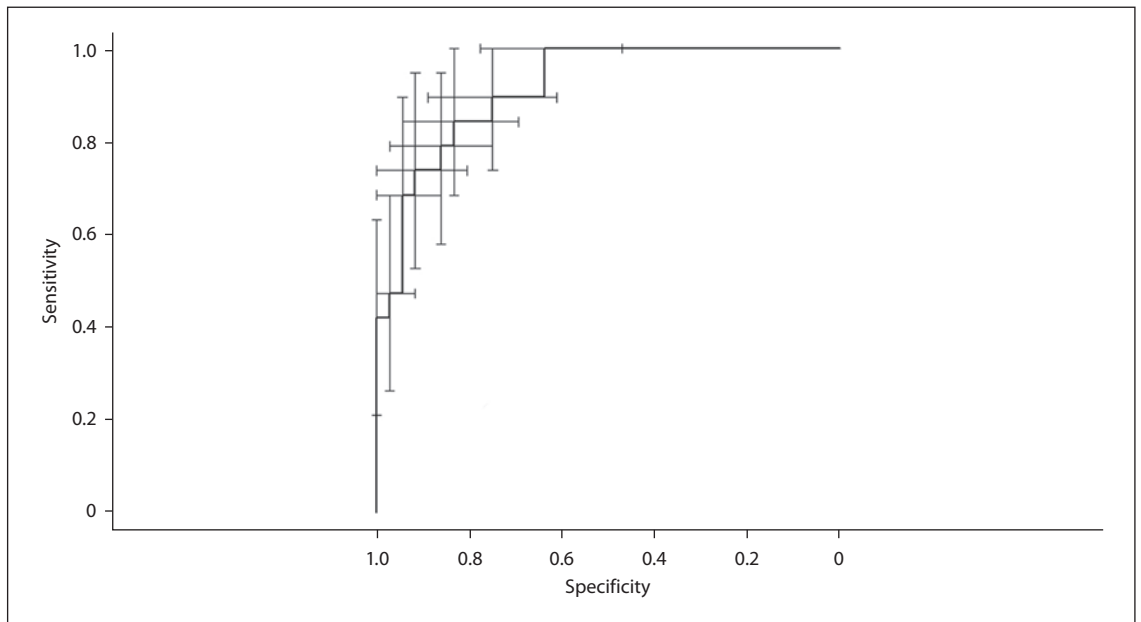**Fig. 1.** Early response as a predictor of poor response at 3 weeks.

Fig. 2. Early response as a predictor of good response at 3 weeks

idly within the first 2 weeks ('early-onset hypothesis') [1]. The time course of antipsychotic response has important implications for medical management of acutely ill patients with schizophrenia and other psychotic disorders. Indeed, the early identification of patients who are likely to do not respond may minimize exposure to ineffective treatment and related side effects and thus may reduce healthcare costs and improve overall outcome in psychotic patients [8]. In the last years, several studies have suggested that early response can predict subsequent re-

sponse and that patients who do not respond to treatment in the first weeks may probably benefit from a change of treatment [4–7, 20–23]. We therefore attempted to replicate these findings in a naturalistic sample of 86 acute psychotic patients treated with haloperidol. Our study confirmed that it is possible to predict antipsychotic response since the first week of treatment: the AUC values were very high both for poor responders and for good responders, while the early response threshold with the best trade-off between sensitivity and specificity was 16 and 23% respectively, with very high values of sensitivities, specificities, positive and negative predictive values. As from a clinical point of view it is more relevant to identify those patients that will be resistant to the current treatment early, the 16% reduction threshold may be more important in daily clinical practice. Our results suggest that this threshold can be used to predict the subsequent patient's response; a failure to achieve a 16% symptom reduction in the first week of treatment indicates that the patient is likely to be resistant at 3 weeks of treatment, and may therefore benefit from a change of treatment. Indeed, our definition of response, derived from the adjusted PANSS total score percentage reduction at 3 weeks of treatment, is related to longer term measures of outcome according to some recent evidence. Particularly, results from a large meta-analysis of literature including 1708 patients revealed that percentage reduction in the first weeks of treatment was significantly higher than the additional change in the BPRS during the rest of the year: 68% of the total BPRS effect was already achieved after only 4 weeks of treatment [24].

Previous research used different symptom improvement thresholds to define early response/non-response, including an absolute lack of symptom improvement (0%) [6, 20], a ≥10% symptom improvement [7], to 20% symptom improvement from baseline on the BPRS or PANSS [4, 5, 21–23]. The time point at which early response/non-response was assessed in previous studies also varied, but most of them focused on the second week of treatment [4, 5, 20, 22, 23]. Therefore, our results allow to confirm and to extend previous findings to the first week of treatment. Our study has several limitations that must be taken into account in the interpretation and generalization of the results. First, the main limitations were the relatively small sample size and the high number of subjects exiting the study that did not allow us to evaluate the predictive power of early response on subsequent response at 4 weeks of treatment. Second, our patients were from markedly to severely ill (mean PANSS score at baseline 104 ± 18) [18]. Thus, if on the one hand our results

clearly demonstrate the early onset of antipsychotic response and its usefulness in daily clinical practice, on the other hand the question of whether patients with different severity would show a similar pattern of response still remains unsolved. Third, our sample included only patients treated with haloperidol, a typical antipsychotic that is often used in the acute phase of psychosis for its fast action [2]. Therefore the extension of our results to other agents is not warranted. Nonetheless, according to the meta-analysis of Agid et al. [1], the observed pattern of response is likely to be similar with other antipsychotic treatment. Furthermore, our patients were treated with a haloperidol monotherapy, thus we can exclude unspecific effects due to symptomatic therapies, like benzodiazepines, in our sample. Finally, 80% of patients were treated with other antipsychotics in the past, thus the observed pattern of response may be altered by previous antipsychotic treatments. Although we cannot exclude this possibility, it seems to be unlikely, because several previous studies on this issue included drug-free or drug-naive patients and uniformly observed a rapid response [25–31]. Further, it should be considered that in our sample the 20% of patients were drug-free at the recruitment.

It should be underlined that our sample included patients treated with variable doses of haloperidol. Therefore, considering that increasing the haloperidol dose up to about 9 mg/day within the first 2 weeks of treatment can lead to a clinical improvement while further increasing do not result in further amelioration [9], we repeated the analysis after exclusion of patients who received an increasing dose within this dose threshold of haloperidol during the first 2 weeks of treatment. Probably due to the low number of those patients (only 3), our results did not change (data not shown).

Conclusions

Our results confirm that early non-response to antipsychotic treatment accurately predicts subsequent non-response to continued treatment with the same antipsychotic agent. A threshold of 16% reduction can be used in clinical practice to identify those patients who are unlikely to respond to antipsychotic therapy. As previously reported, identifying early non-responders is an important step in the management of patient with schizophrenia and other psychotic disorders since it can help to minimize exposure to suboptimal or ineffective treatment strategies, reduce healthcare costs and improve overall outcome in psychotic patients [8].

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