Research Article

Early antipsychotic response predictors in schizophrenia: a naturalistic study

Abstract

Studies on schizophrenia failed to find predictors of antipsychotic response, early response apart. We therefore hypothesized that early responders (ERs) could be identified by specific clinical characteristics. Two independent samples of schizophrenic patients were analyzed. Further, analyses were repeated merging the two samples (total=171). Factors associated with early response were also analyzed in patients taking first and second generation antipsychotics (FGAs and SGAs). A t test or a wilcoxon test was used to detect significant differences between ERs and early non responders (ENRs). In the investigation sample ERs had a lower illness duration (p=0.02), suffered from more severe positive (p=0.01), general (p=0.01) and hostile avoidance, that is represented by impulsivity, excitement, hostility and uncooperativeness, (p=0.01); these results were substantially confirmed in the replication sample and in the two samples merged. Results obtained in FGAs-treated patients were similar to those observed in the whole sample. In patients taking SGAs, ERs had more severe positive and depressive symptoms, without differences among other factors. In line with previous findings, the most relevant difference between ERs and ENRs was in the age, ERs being with a natural tendency younger (mean age ERs=39.6, ENRs=49.5). Regarding FGAs/SGAs differences, our results suggest that in ENRs treated with FGAs an increase of antipsychotic drug dosage seems to be of scarce benefit. Switching to a SGA might be of more clinical usefulness.

Keywords: schizophrenia, antipsychotics, schizophrenia response, antipsychotics response

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Introduction

Schizophrenia is a complex psychiatric disorder affecting approximately 1% of the population worldwide.[1] Overall, it reduces the individual lifespan by on average of 15–20years.[2] Schizophrenia is characterized by a heterogeneous outcome, with a smaller proportion (20–50%) of patients experiencing recovery or significant improvement, compared to a majority of them with a course characterized by multiple episodes and increasing impairment.[3]

Several premorbid and postmorbid factors have been associated with outcome in schizophrenic patients. Predictors of a better outcome include female gender,[4,5] being married at the onset of the illness,[5,6] later onset, acute onset [5], and the presence of a psychological stressors preceding the onset.[7] On the other hand, predictors of poor outcome include a family history of schizophrenia,[8] poor premorbid functioning,[6,9,10] lack of insight,[6,9] severe negative symptoms,[4] a long duration of untreated psychosis[11] and substance misuse.[12] Nonetheless, the prognostic value of these variables remains unclear since several studies failed to find any association between outcome and the above-mentioned factors.[7,13]

According to the "early onset hypothesis" of antipsychotic action, an increasing number of studies showed that the early response to antipsychotics is a very robust predictor of long-term outcome.[14–21] Early response is defined in different manners by different Authors. For example in 2008 Kinon et al.,[18] evaluated early response using the definition as >20% Positive and Negative Syndrome Scale (PANSS) total score improvement at week 2; in 2011 Schennach-Wolff et al.,[22] considered early response as a >30 % PANSS total score reduction within the first two weeks. Furthermore, in a previous work conducted by our Research Group, we reported that it is possible to predict antipsychotic response since the first week of treatment; particularly,

a 23% PANSS score reduction at the first week of treatment was associated to subsequent response, with a specificity of 83% and a sensitivity of 90%.[16] In the present study, we decided to apply the threshold identified in our previous work since it was identified in a sample of patients very similar to the ones investigated here (similar inclusion and exclusion criteria).

The identification of clinical factors associated with treatment outcome in schizophrenia could have considerable benefits in clinical practice. Indeed, early identification of poor responders may allow avoiding ineffective treatments and related side effects. Further, since some predictors are correctable, their detection may provide specific treatment targets. A better comprehension of the factors related to poor/good response might finally help to better understand the underpinning pathophysiology of the disease. Nonetheless, as yet studies failed to find clear predictors of long term response as exposed above, early antipsychotic response apart. On the other hand, we could hypothesize that early response itself may be affected by other factors, as recently suggested by some Authors. Particularly, a recent study by Levine et al. showed that factors associated with a good improvement during the first two weeks of treatment were male gender, younger age and a diagnosis of paranoid schizophrenia.[23] Furthermore, in a naturalistic, multicenter study, Schennach-Wolff et al.,[22] identified several early-improvement factors; for instance, they showed that early improvers were more often first-episode patients, with a shorter duration of illness and a shorter duration of the present episode. However, despite the possible clinical relevance, until now only a few number of studies compared early responders (ERs) with early non-responders (ENRs) in order to detect clinical and socio-demographic factors associated with outcome.

Taking into account the promising results of these studies, in the present paper we compared ERs and ENRs for a wide range of

socio-demographic and clinical factors in two independent samples of schizophrenic patients. Further, possible predictors of early response were separately analyzed in patients taking first and second generation antipsychotics (FGAs and SGAs), in order to compare factors associated with early response in the two groups of drugs.

Methods

Investigation sample

The present work was conducted in a naturalistic setting and it has to be considered an observational study. Patients were enrolled into the study when admitted at the Psychiatric Unit, Department of Psychiatry, and University of Bologna, Italy. Inclusion criteria were age from 18 to 75 and a diagnosis of schizophrenia according to DSM-IV-TR criteria and confirmed by the administration of the Structured Clinical Interview for DSM-IV-TR axis I disorders (SCID-I). Patients were included if they needed the introduction or the change of the previous antipsychotic treatment. They were treated according to the current clinical practice, without any limitation concerning the kind of antipsychotic or the dosage. Exclusion criteria were the presence of severe medical conditions or moderate to severe dementia (Mini Mental State Examination score <20). Clinical and demographic characteristics of patients were assessed at the recruitment. The Positive and Negative Syndrome Scale (PANSS) was administered weekly during the hospitalization by senior psychiatrists; inter-rater evaluation gave reliable results (k>0.80).

Written informed consent was obtained for each patient recruited. The study protocol was approved by the local Ethical Committee and it has been performed in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki.

Replication sample

Data of the replication sample were previously reported in a pharmacogenetic study.[24] Seventy-one psychotic patients were enrolled in the Department of Psychiatry Teaching Hospital Maribor, affected by schizophrenia or schizoaffective disorders according to the DSM-IV-TR criteria. Starting treatment was haloperidol or risperidone based on clinicians' choice. Drugs doses were also based on clinicians' experiences and the study was conducted on a naturalistic basis. Patients who received depot antipsychotics in the last 4weeks and patients who were receiving other antipsychotics in the last 2weeks were not included. Other exclusion criteria were a lifetime history of substance misuse and/or the presence of hepatic diseases, concomitant medications with the exception of anti cholinergic agents, and a severe or unstable medical or neurological disease that could impair evaluations. The study was approved by The Slovenian Ethics Committee for Research in Medicine and written consent was obtained from all the patients. The study was carried out in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki. The patients were examined by two experienced psychiatrists; inter-rater evaluation gave reliable results (k>0.80).

Psychopathological symptoms were assessed with the Brief Psychiatric Rating Scale and with Clinical Global Impression at two time points: 8–12days after the first administration of antipsychotic drug and after 4weeks of treatment. Patients were observed for a period of 4weeks.

Statistical analyses

Patients were divided into ERS and ENRs according to the percentage symptoms reduction at one week of treatment, calculated using the formula P% = (P0–P1)/P0 x100, where P0 was PANSS score at baseline and P1 was PANSS score at 1 week of treatment. In the replication sample, the BPRS percentage reduction was used instead of the PANSS. A t test or a wilcoxon test, according to the type of variables, was used to detect significant differences between ER and ENR patients. For both the two samples included, analyses were performed both on the whole sample and in the two subsamples of patients taking FGAs and SGAs.

According to our previous work, a threshold of 23% was used for the definition of ER and ENR patients; as stated above,[16] this threshold represents the percentage symptoms reduction at one week of treatment with the best trade-off between sensitivity and specificity. According to the suggestion by Obermeier et al.,[25] and Leucht et al.[26] PANSS scores were corrected by subtracting 30 points (the minimum value of PANSS scale) to every PANSS score before calculating percent changes.

In the investigation sample, the following variables were investigated: sex, age, age at onset, illness duration, education (expressed in educational years), employment, psychiatric family history, medical co-morbidities, number of psychotic episodes, number of previous hospitalizations, age at the first hospitalization, duration of hospitalizations, age at onset, substance abuse, previous suicide attempts, number of previous suicide attempts, age at first suicide attempt, presence and type of life events, antipsychotic dosage (expressed in chlorpromazine equivalents). Further, we also considered the following PANSS scores at baseline: total, positive, negative, general subscales and PANSS clusters positive, negative, disorganized/concrete, excited and depressed as defined from Wallwork et al.,[27]

In the replication sample, the following variables were investigated: sex, age, illness duration, number of hospitalizations, medical co-morbidities, and BPRS score at baseline.

Finally, the analyses were repeated merging together the two samples in order to evaluate potential differences in results and potential bias related to single sample features. For this last analysis, BPRS and PANSS scores were converted into CGI scores according to the suggestions by Leucht et al.,[28,29]

Results

Investigation sample

A total of 97 patients were enrolled in the investigation sample. Clinical and demographic characteristics of the sample are reported in (Table 1). The main results are reported in (Table 2 and 3). Results on other predictors are available upon request.

ER patients had higher scores in the positive (mean score ER=25, ENR=21.3; p=0.01) and general (mean score ER=45.1, ENR=39.8; p=0.01) subscales of the PANSS and in the excited cluster (mean score ER=11, ENR=8.1; p=0.01). Further, they had a lower illness duration (mean duration ER=13.5 months, ENR 20.8 months; p=0.02).

Among patients taking FGAs, ERs had higher PANSS total (mean score ER=91.6, ENR=75.2; p=0.03), general (mean score ER=45, ENR=36.4; p=0.03) and positive scores (mean score ER=26.5, ENR=19.4; p=0.01); further, they had a lower illness duration (mean duration ER=5.4months, ENR=28.8months; p=0.03) and a lower age (mean age ER=42.4 years, ENR=53.9; p=0.02).

Among patients taking SGAs, the only differences between ERs and ENRs were related to psychopathology at baseline: ERs had

higher PANSS positive scores (mean score ER=13.8, ENR=11; p=0.03) and higher depression cluster scores (mean score ER=8.1, ENR=5.8; p=0.02) compared with ENRs. Drug dosages, expressed in chlorpromazine equivalents, did not differ among ERs and ENRs.

Table 1 Clinical and demographic characteristics of the investigation sample (n=97)

Variable	Results
Age (years) (mean±SD)	42.3±14.2
Sex	M=56 (57.7%)
Age at onset (years) (mean±SD)	25.8±9.5
Disease duration (years) (mean±SD)	16.3±14.7
PANSS total score at baseline (mean±SD)	87±20.4
PANSS positive score at baseline (mean±SD)	23.5±6.9
PANSS negative score at baseline (mean±SD)	20.0±8.6
PANSS general score at baseline (mean±SD)	43.0±11.0
Number of episodes (mean±SD)	2.8±3.2
Number of hospitalizations (mean±SD)	2.7±2.7
Education (years) (mean±SD)	12.2±4.8
Medication	FGAs=45 (46.3%); SGAs=52 (53.6%)

Table 2 Early responder/non responder comparison in the investigation and in the replication sample

	Early Responder	Non Early Responder	p-Value
Investigation Sample			
PANSS TOT baseline	89.8	82.6	0.08
PANSS POS baseline	25	21.3	0.01
PANSS NEG baseline	19.6	20.7	0.52
PANSS GEN baseline	45.1	39.8	0.01
CLUSTER POS baseline	14.8	14	0.4
CLUSTER NEG baseline	13.5	15.2	0.2
CLUSTER DIS baseline	9.1	8.3	0.3
CLUSTER EXC baseline	11	8.1	0.01
CLUSTER DEP baseline	8.4	7.1	0.07
Age (years)	40.2	45.5	0.07
Illness Duration (months)	13.5	20.8	0.02
Replication Sample			
BPRS TOT baseline	26.2	25.5	0.8
Age (years)	31.2	37.6	0.02
Illness Duration (months)	55.2	76.5	0.3
Medication Dosage	195.3	277.3	0.1
(chlorpromazine equivalents)			
Investigation+Replication Sample			
CGI TOT baseline	3.3	2.5	0.01
Age (years)	39.6	49.5	0.08
Illness Duration (months)	130.3	135.4	0.8
Medication Dosage	296.9	274.9	0.4
(chlorpromazine equivalents)			

Replication sample

A total of 74 patients were enrolled in the replication sample. Clinical and demographic characteristics of the sample are reported in (Table 4). The main results are reported in (Table 2 and 3). Results on other predictors are available upon request.

ER patients had lower age (mean age ER=31.2years, ENR=37.6; p=0.02). Other clinical characteristics were not significantly different between the two groups of patients.

Among patients taking haloperidol, ER patients had a lower age compared to ENRs; in line with the results obtained in the investigation sample, ER and ENRs taking SGAs (risperidone in this sample) did not differ for any of the factors investigated. Again, no differences were found in drug dosages expressed in chlorpromazine equivalents.

Investigation replication sample

The differences in findings between the investigation sample and the replication sample could be explained by several reasons, such as sample size and assessment tools. The two samples were so merged in order to increase the power of the sample after conversion of BPRS and PANSS scores into CGI scores according to the suggestions by Leucht et al.,[28,29]

The main results are reported in Table 2 and 3. Results on other predictors are available upon request.

Compared with ENR patients, ER had higher CGI scores (mean score ER=3.3, ENR=2.5; p=0.01).

Among patients taking FGAs, ERs were taking lower drug dosages (p=0.03) and they were significantly younger compared with ENRs (mean age ER=39.6 years, ENR=47.6; p=0.003). Among patients taking SGAs, ERs had higher CGI scores at baseline (mean score ER=4.1, ENR=1.9; p=0.03).

Discussion

Clinical research on schizophrenia identified several predictors of better outcome in schizophrenic patients, including female gender,[4,5] later and acute onset of the disease.[5] However, other studies failed to find any association between outcome and the above-mentioned factors,[7,13] making their clinical usefulness very poor. The reasons for these discrepancies could be numerous: firstly, the sample selections are quite different among studies, varying from very strictly criteria to observational studies; secondly, several clinical variables that could modify the antipsychotic response are often not properly take into account or not adequately assessed (e.g. the presence of Axis II co-morbidity, the pharmacological compliance, etc.); thirdly, each antipsychotic has some unique pharmacodynamic profile which may be accountable for different effective profile in specific subgroup of patients; therefore, studies should be ideally performed using a low number of drugs which could be analyzed separately. Unfortunately, this is not possible in naturalistic setting or in small samples.

On the other hand, in the last years it was repeatedly demonstrated that early antipsychotic response is a strong predictor of subsequent response.[14–21] We therefore hypothesized that ER patients could represent a distinct subgroup of patients, identified by specific clinical and demographic characteristics. Therefore, the aim of the present study was to identify socio-demographic and clinical factors associated with early improvement in antipsychotic-treated patients. Further, we aimed to compare factors associated with early response in patients taking FGAs and SGAs.

Our results showed that main differences observed between ERs and ENRs are related to factors associated with illness chronicity and baseline psychopathology. Particularly, in the investigation sample ERs suffered from more severe positive, general and excited symptoms compared to ENR patients. These findings could not be confirmed in the replication sample since psychopathology was assessed with

the BPRS instead of the PANSS, not allowing the symptom cluster analysis. However, when the analyses were conducted on the two samples merged together, CGI scores were significantly higher among ER patients. Several previous studies reported similar results. Recently, Schennach-Wolff et al.,[22] & Crespo-Facorro et al.,[30] reported that suffering from more severe positive symptoms at baseline predicts achieving early improvement. Previously, Palao et al. found that among other clinical and socio-demographic factors, exclusively the severity of positive symptoms predicted a better response to treatment in acute exacerbations.[31]

Table 3 Early responder/non-responder comparison among patients taking FGAs and SGAs

Patients Taking FGAs				Patients Taking SGAs			
	Early Responder	Non Early Responder	p		Early Responder	Non Early Responder	p
Investigation Sample							
PANSS TOT baseline	91.6	75.2	0.03	PANSS TOT baseline	95.5	90.2	0.4
PANSS POS baseline	15.2	14	0.3	PANSS POS baseline	26.2	23	0.1
PANSS NEG baseline	17.3	14.8	0.2	PANSS NEG baseline	20.3	23.5	0.2
PANSS GEN baseline	45	36.4	0.03	PANSS GEN baseline	48.9	43.6	0.1
CLUSTER POS baseline	26.5	19.4	0.01	CLUSTER POS baseline	13.8	11	0.03
CLUSTER NEG baseline	20.1	19.3	0.8	CLUSTER NEG baseline	19.7	15.3	0.1
CLUSTER DIS baseline	9	8.1	0.2	CLUSTER DIS baseline	8	7.2	0.2
CLUSTER EXC baseline	11.2	10.7	0.7	CLUSTER EXC baseline	8.6	8.1	0.6
CLUSTER DEP baseline	9.3	8.3	0.2	CLUSTER DEP baseline	8.1	5.8	0.02
Age	42.4	53.9	0.02	AGE	37.3	38.7	0.7
Illness Duration	15.4	28.8	0.03	Illness Duration	10.1	14.1	0.3
Replication Sample							
BPRS TOT baseline	45.5	56.2	0.1	BPRS TOT baseline	25.8	22.7	0.2
Age (years)	33.8	47.6	0.01	AGE	30.4	35.4	0.1
Illness Duration (months)	79.5	109.3	0.5	Illness Duration	47.6	69.2	0.4
Medication Dosage (chlorpromazine equivalents)	195.3	277.3	0.1	Medication Dosage (chlorpromazine equivalents)	186.8	191.8	0.7
Investigation+Replication Sample							
CGI TOT baseline	4.3	4.1	0.4	CGI TOT baseline	4.1	1.9	0.03
Age (years)	39.6	49.5	0.003	AGE	34.6	37.4	0.2
Illness Duration (months)	160.4	221.3	0.2	Illness Duration	91	109.9	0.4
Medication Dosage (chlorpromazine equivalents)	274.3	327.4	0.3	Medication Dosage (chlorpromazine equivalents)	277.3	250.2	0.4

Table 4 Clinical and demographic characteristics of the replication sample (n=74)

Variable	Results
Age (years) (mean±SD)	35.5±11.8
Sex	M=54 (72.9%)
Age at onset (years) (mean±SD)	25.8±9.5
Disease duration (months) (mean±SD)	69.3±9.5
BPRS total score at baseline (mean±SD)	25.8±11
Number of episodes (mean±SD)	2.8±3.2
Medication	haloperidol=15 (20.2%); risperidone=59 (79.8%)

Our main finding about premorbid characteristics is that longer illness duration is associated with a lower likelihood to achieve early antipsychotic response. The difference was significant in the investigation sample, and a trend was observable in the replication sample and in the merged sample. Several studies reported that a longer duration of illness predicts a poorer outcome in patients with schizophrenia, maybe reflecting the existence of progressive brain deterioration during the illness that leads to a gradual loss of treatment response.[5,30]

Regarding socio-demographic variables, not surprisingly ER patients were found to be younger compared with ENRs. The difference was significant in the replication sample and a trend for a younger age was observed both in the investigation sample as well as when the two samples were merged together. Concerning gender, we did not find any difference between ER and ENR patients. Previous research on this issue reported conflicting results, with some studies reporting a better outcome in men[23] and other in women.[32] In this case, some Authors suggested a possible protective role for estrogens through a direct anti-dopaminergic effect, although data are still lacking to draw definitive conclusions about this hypothesis.[33]

When analyses were conducted only on patients taking FGAs, our results were very similar to the ones observed in the whole sample. Particularly, in the investigation sample, patients showing an early improvement to FGAs were younger, had a lower illness duration and a higher total PANSS score at baseline; further, they suffered from more severe positive and general symptoms. Interestingly, these results were not replicated among patients taking SGAs; in this subgroup of patients, ERs had more severe positive and depressive symptoms compared with ENRs, without significant differences among other clinical and socio-demographic factors. In the light of these findings, we can hypothesize that other variables not investigated in the present study, such as genetic factors, could play a role in SGA response. Further, the higher proportion of depressive symptoms among ER

patients confirms that SGAs have a greater efficacy on depression compared with FGAs, a finding that was previously reported by several Authors.[34,35]

Taken together, our results suggest that patients with a higher age, longer illness duration and a lower severity in positive, total and general symptoms might show a worse pattern of response to FGAs. Considering that the medication dosage did not differ among ERs and ENRs, it seems unlikely that the better pattern of response observed in ERs was due to higher medication doses. Therefore, we can conclude that in this subgroup of patients an increase of antipsychotic drug dosage seems to be of scarce benefit, while a switch to a SGA might be of more clinical usefulness. Similar results were previously reported by Schennach-Wolff et al. [22]. Similarly, we previously showed that increasing the haloperidol dose over the threshold of about 9 mg/day in the absence of response after 14days of treatment is not effective and may be rather associated only with an increased risk of side effects.[36]

The main limitation of the present study is the relatively small sample size (97 subjects in the investigation sample). In order to reduce the impact of this limitation, our findings were replicated in a second sample and also on the two samples merged together. Despite the different psychopathological assessment tool used in the studies (PANSS in the investigation sample and BPRS in the replication one), complicating the comparability of the results, the major outcomes of the investigation sample were substantially confirmed in the replication and in the combined sample.

The naturalistic study design represents both strength and a limitation of the present work. On one hand, the lack of homogeneity in the clinical variables limits the generalization of the findings. Further, this design does not allow a sufficient control of results for the effect of different pharmacological treatments. On the other hand it represents a real-world situation, making results more closed to general clinical setting compared with randomized-controlled trials. Further, it allowed us to investigate clinical factors in patients treated with different antipsychotic medications at different dosages.

Conclusion

In the last years, it was repeatedly demonstrated that early improvement during antipsychotic treatment is a strong predictor of subsequent response. In the present study, subjects suffering from more severe positive, general and excited symptoms, being younger and having shorter illness duration showed more favorable early response. Among patients treated with SGAs, having more positive and depressive symptom were the only factors associated with early response. On the other hand, patients who showed a better pattern of response to FGAs were characterized by having a lower age, a shorter illness duration and higher severity in positive, total and general symptoms. Interestingly, in ENR patients taking FGAs an increase of antipsychotic drug dosage seems to be of scarce benefit, while a switch to a SGA might be of more clinical usefulness. The identification of predictors of early antipsychotic response would be of great clinical interest since it would prevent unnecessary exposure to ineffective treatments, diminish the risk of adverse events and reduce the duration of hospitalization, illness-related costs and global burden.

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Conflicts of interest

Author declares there are no conflicts of interest.

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