Schizophrenia resistance: is there a difference?

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Received 6 October 2010
Accepted 15 March 2011

Egyptian Journal of Psychiatry 2013, 34:51–60

Background
Schizophrenia is a chronic disease of the body and mind that affects 1% of the population. About one-fifth to one-third of all patients with schizophrenia do not respond adequately to drug treatment and that have been consistent over time. Definitions of this group have long been hampered by a lack of consistency with confusion with chronicity. Clozapine has shown superior efficacy and this has been replicated consistently.

Aim and objectives
Because of the high prevalence, importance, and inconsistency of schizophrenia resistance, the current study aimed to (a) examine the differences between resistant and nonresistant schizophrenic groups in chronic long-stay patients, (b) study the clinical profile of the clozapine-resistant group in comparison with others, and finally (c) determine the predictors of resistant schizophrenia.

Methods
This was a retrospective and cross-sectional study of 95 patients with chronic schizophrenia or schizoaffective disorder, admitted in long-stay hospital wards at the Psychological Medicine Hospital (Kuwait). They were interviewed by Structured Clinical Interview for DSM-IV and diagnosed according to the *Diagnostic and Statistical Manual of Mental Illness*, 4th ed. criteria. Patients were assessed by the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Severity (CGIS) scale, and Mini-Mental State Examination. Sociodemographics, clinical characteristics, and the history of treatment were determined. Schizophrenia resistance was formulated according to modified Kane's criteria, which include the following: BPRS score of at least 45; two or more of positive symptoms score of at least 4 (suspiciousness, hallucinatory behavior, conceptual disorganization, and unusual thoughts); CGIS score of at least 4 (moderate to extremely ill); previous failure on two antipsychotic trials of different categories of the full therapeutic range ($\geq$1000 mg of chlorpromazine equivalent) and for at least 3–6 months' duration; and finally, no preceding good function for at least 2.5 years in the last 5 years.

Results
Thirty-six patients fulfilled the criteria of schizophrenia resistance (37.8%). There was a significant shift in the drug regimen prescribed, with the prescription of more atypical antipsychotics, especially clozapine, with repeated failure of previous drug trials. The only significant difference between the resistant and the nonresistant group was in the psychopathological severity, indicated by higher scores on PANSS, and CGIS scores. Age younger than 40 years and early onset age of schizophrenia ($<$20 years) were powerful predictors for schizophrenia resistance; other sociodemographic and clinical characteristics lacked significant predictive value.

Conclusion and recommendation
Younger age and early-onset schizophrenia are considered poor prognostic factors. Early aggressive management of schizophrenia may help eliminate chronicity as well as resistance. Research on the biological predisposition for schizophrenia resistance including the clozapine resistance group is required.

Keywords:
clozapine, resistance to antipsychotics, schizophrenia

Egypt J Psychiatr 34:51–60

1110-1105

Introduction

Schizophrenia is a chronic disease of the body and the mind that affects 1% of the population. Schizophrenia should be understood at least from two perspectives: first, considering the integration of the individual into the society and second, schizophrenia is a medical problem that can be treated with medications and psychotherapies

(Quintero *et al*., 2011). There is a large group of patients with 'treatment-resistant schizophrenia' (TRS), that is cases in which the minimum degree of remission with conventional treatments is not achieved. This indicates that even today, we lack an integrative treatment model that combines specific interventions with variable effectiveness. The concept of TRS should have evolved with advancement in the currently available knowledge and therapeutic response (Quintero *et al*., 2011).

Between one-fifth and one-third of all patients with schizophrenia do not respond adequately to drug treatment. Reports of the proportion of patients with drug resistance have been consistent over time (Prien and Cole, 1968; Davis and Casper, 1977; Essock *et al*., 1996), and the treatment of these patients has remained a persistent public health problem. Treatment-resistant patient are often highly symptomatic and may require extensive periods of hospital care (McGlashan, 1988). This involves a disproportionately high cost (Revicki *et al*., 1990). These formed the basis for interest among clinicians following the demonstration of clozapine's efficacy in inpatients with TRS (Kane *et al*., 1988).

Studies of TRS have long been hampered by a lack of consistency in definition. Commonly, TRS was considered roughly equivalent to chronic or frequent hospitalization (Holden *et al*., 1968; Small *et al*., 1975; Ruskin *et al*., 1979; Carman *et al*., 1981; Wolkowitz *et al*., 1986). However, chronic hospitalization can occur despite a low level of symptoms (McGlashan, 1988). Current and persistent positive symptoms of psychosis and at least a moderate overall severity of current illness should also be used to define nonresponsiveness (Meltzer, 1990). Chronicity alone cannot predict the likelihood of response to a treatment regimen with antipsychotics (Brenner *et al*., 1990; Christison *et al*., 1991).

Using parameters to define poor outcome, some authors have used the number of rehospitalizations or chronic hospitalizations to define TRS. However, factors such as poor compliance, weak social support programs, or a history of violence may also result in long-term hospitalization of patients who do not have TRS (Elkis and Meltzer, 2010). For most researchers, the concept of TRS has a precise meaning. It is the persistence of positive symptoms, which are moderate or severe, after a correct biological treatment (Peuskens, 1999). Recent publications have used the following expressions: ultraresistant schizophrenia (Mouaffak *et al*., 2006), clozapine-resistant schizophrenia (Havaki-Kontaxaki *et al*., 2006), Pharmacological TRS (Enguix and Fernández, 2006), and neuroleptic-nonresponsive schizophrenia (Meltzer, 1992).

In accordance with these close definitions, it would be erroneous to classify a patient who does not follow the treatment as TRS, stating that resistance would be then due to the patient and not to the schizophrenic disease (Elkis and Meltzer, 2007). This statement is useful to investigate the efficacy of the drugs.

The landmark trial of Kane *et al*. (1988) showed superior efficacy of clozapine over other antipsychotic agents, a finding that has been replicated consistently (Chakos *et al*., 2001; Lewis *et al*., 2006; McEvoy *et al*., 2006) in studies that examined the subgroups of medication-resistant patients. Although clozapine is considered the most efficient antipsychotic agent in refractory patients, as many as 40–70% of these patients show only a poor or a partial response, even with adequate blood levels of clozapine (Kane *et al*., 1988; Meltzer *et al*., 1989; Lieberman *et al*., 1994; Tollefson *et al*., 2001).

Methods

The current study was carried out at the psychological medicine hospital, the only psychiatric hospital in the State of Kuwait. The researchers examined 127 patients who had been hospitalized for a long time ($\geq$6 months) in the chronic wards of the hospital. All patients were examined after oral/written consent was obtained from the patients and/or their families. Approval from the local research ethical committee was obtained.

Inclusion criteria

Patients at least 18 years of age, those with schizophrenia and schizoaffective disorder, both sexes, and treatment-resistant and nonresistant patients were included.

All patients were subjected to a Structured Clinical Interview using SCID (First *et al*., 1995) and were diagnosed according to the *Diagnostic and Statistical Manual of Mental Illness*, 4th ed. to confirm the diagnosis. Only 95 patients were found to have schizophrenia or schizoaffective disorder.

The study was carried out in two phases:

Retrospective phase

In this phase, the files of the patients were reviewed to collect data on all clinical data socio demographic and treatment characteristics of patients with schizophrenia or schizoaffective disorder.

Cross-sectional phase

Patients were subjected to the following psychometric ratings, carried out by two different raters for more reliability: the Positive and Negative Syndrome Scale (PANSS), which includes 30 items on three subscales: seven items covering positive symptoms, seven items covering negative symptoms, and 16 items covering general psychopathology. Each item was scored on a seven-point item-specific scale ranging from 1 to 7; thus, the positive and negative subscales each ranged from 7 to 49, and the general psychopathology scale ranged from 16 to 112. It is a standard tool for assessment of clinical outcome in treatment studies of psychotic disorders and useful for the assessment of severity in clinical practice (Kay *et al*., 1986). The Brief Psychiatric Rating Scale was used, which is a short scale for measuring the severity of psychiatric symptomatology. It includes 18 items that are rated on a seven-point item-specific scale from 0 to 6, with the total score ranging from 0 to 108 (Overall and Gorham, 1962). The Clinical Global Impression Severity

(CGIS) scale was used, which is rated on a seven-point scale, measuring the severity of illness using a range of responses from 1 (normal) to 7 (the most severely ill) (Guy and Bonato, 1970). Finally, the Mini-Mental State Examination (MMSE) was used, which is a 30-point cognitive test developed for the bedside assessment of cognitive functions including orientation, memory, attention, construction, and language (Folstein *et al.*, 1975).

Criteria for treatment-resistant schizophrenia according to Kane *et al.* (1988)

In the current study, the researchers used the Kane *et al.*'s (1988) criteria to define resistant cases. According to Kane, for the classification of a schizophrenic patient as treatment resistant, he/she should fulfill the following criteria:

(1) Historical: at least three drug trials of different chemical classes with doses equivalent to 1000 mg/day chlorpromazine for a period of 6 weeks, without significant relief.
(2) No period of good function in the preceding 5 years ($\geq$2.5 years)
(3) Actual:
    (a) A score of at least 45 in the Brief Psychiatric Rating Scale (1–7 degree of severity), with scores of at least 4 in two of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content.
    (b) CGIS more than or equal to 4 (moderately ill).

For practical reasons according to the clinical characteristics of our sample, modified criteria were applied as follows: (a) previous two drug trials with nonresponsiveness and (b) Previous treatment for at least 3–6 months with doses equivalent to 400–1000 mg/day chlorpromazine.

Statistical analysis

Data were collected and coded, and then entered into an IBM compatible computer, using the SPSS version 17 (International Business Machine Company, Armork, NewYork, USA); the data entered were checked for accuracy and then for normality using the Kolmogorov–Smirnov test. Qualitative variables were expressed as number and percentage, whereas quantitative variables were expressed as the mean ($\bar{x}$) and SD. The arithmetic mean ($\bar{x}$) was used as a measure of central tendency, whereas SD was used as a measure of dispersion.

The following statistical tests were used:

Independent-samples *t*-test was used as a parametric test of significance for comparison between two sample means after performing the Levene's test for equality of variances.

The χ^2-test (or likelihood ratio) was used as a nonparametric test of significance for comparison between the distribution of two qualitative variables.

Fisher's exact test was used as a nonparametric test of significance for comparison between the distributions of two qualitative variables whenever the χ^2-test was not appropriate; it yields the *P*-value directly.

Paired-sample *t*-test was used as a parametric test of significance for comparison between before and after values of quantitative variables.

One-way analysis of variance (*F*-test) was used as a parametric test of significance for comparison between more than two sample means using either Scheffe's or Tauhane's post-hoc tests for results of homogeneity testing.

The Pearson correlation coefficient (*r*) was used as a parametric measure of the mutual relationship between two normally distributed quantitative variables.

The Cochran test was used for comparison between categories and differential types of antipsychotics used in the three phases of treatment.

Logistic regression analysis was used to detect significant predictors of resistant schizophrenia according to Kane's criteria.

A 5% level was chosen as a level of significance in all the tests used.

Results

On studying the 127 patients who were in the long-stay wards of the hospital, only 95 patients were found to have the diagnosis of schizophrenia or schizoaffective disorder. Those who were not diagnosed with schizophrenia (23 patients had mental subnormality, eight patients had nonschizophrenic psychosis, and one had personality disorder) were excluded. On the basis of Kane *et al.*'s criteria for the identification of patients with TRS after modification, only 59 patients (62.10%) were considered to be nonresistant, whereas 36 patients (37.89%) were found to be treatment resistant.

Sociodemographics and clinical characteristics (morbidity profile)

The sociodemographic data indicated that 84.21% of the patients were men, 32.6% were not working, 71.6% were single, and only 21% had a high level of education. Most of the patients (90%) were of very low or low socioeconomic standard, around 25% had no available private house, 50.5% of the studied sample had a positive family history of psychiatric illness, and only 31.7% had a family history of medical illness, that is diabetes mellitus, hypertension, or dyslipidemia (Tables 1 and 2).

Positive psychiatric symptoms were found in 72 patients (75.8%) at the onset of illness and undifferentiated schizophrenia or paranoia were the most common diagnoses (43.2 and 29.2%), respectively (Table 2).

In terms of medical comorbidities, 28 patients (29.47%) had diabetes, 29 patients (30.5%) had hypertension, and 46 patients (48.42%) had dyslipidemia. Half of the patients ($n = 49$, 51.57%) were obese, with a BMI of at least 30. No significant difference was found between the resistant and the nonresistant groups of patients in any of the above-mentioned items ($P > 0.05$).

Table 1 Sociodemographic characteristics of definite resistant and non resistant patients (*n*=95)

Item	Nonresistant (*n*=59)	Definite resistant (*n*=36)	Total (*n*=95)	Pearson's χ^2 (3) LLR χ^2 (3)
Sex				
Female	11	4	15	0.329
Male	48	32	80	
Marital status				
Single	38	30	68	0.157
Married	9	3	12	
Divorced	10	3	13	
Widow	2	0	2	
Job history				
Jobless	40	29	6	0.282
Professional	1	0	1	
Retired	18	7	25	
Education				
Illiterate	15	7	22	0.829
Low grade	32	21	53	
High grade	11	6	17	
University	1	2	3	
Socioeconomic standard				
Very low	20	6	26	0.152
Low	34	26	60	
Moderate	5	3	8	
High moderate	0	1	1	

LLR, log-likelihood ratio.

Table 2 Clinical characteristics of definite resistant and nonresistant schizophrenic patients (*n*=95)

Item	Nonresistant (*n*=59)	Resistant definite (*n*=36)	Total	Pearson's χ^2 (3) LLR χ^2 (3)
Symptoms at onset				
Positive symptoms	44	28	72	0.23
Negative symptoms	3	0	3	
Mixed symptoms	12	8	20	
Clinical diagnosis of schizophrenia				
Undifferentiated	27	14	41	0.92
Paranoid	11	11	22	
Residual	11	3	14	
Disorganized	3	7	10	
Schizoaffective	7	1	8	
Family history of psychiatric illness				
Negative history	30	17	47	0.73
Positive history	29	19	48	
Family history of medical illness (DM, HTN)				
Negative history	42	23	65	0.45
Positive history	17	13	30	

DM, diabetes mellitus; HNT, hypertension; LLR, log-likelihood ratio.
Significant if $P<0.05$.

Table 3 Comparison between categories and differential types of antipsychotics used to treat 95 patients with chronic schizophrenia through three phases of treatment

	Number (%)			
	Trial I treatment	Trial II treatment	Current treatment	Cochran's test
Conventional	81 (85.3)	36 (37.9)	23 (24.2)	
Haldol	21 (22.1)	0 (0)	1 (1.05)	
Trifluoperazine	46 (48.4)	13 (13.6)	1 (1.05)	
Sulpiride	11 (11.5)	19 (20)	19 (20)	
Pimozide	3 (3.1)	4 (4.2)	2 (2.1)	
Atypical	14 (14.7)	49 (51.5)	72 (75.7)	0.00
Clozapine	3 (3.2)	8 (8.4)	37 (38.9)	
Risperidone	5 (5.2)	26 (27.3)	20 (21.05)	
Olanzapine	4 (4.2)	9 (9.5)	7 (7.3)	
Quetiapine	2 (2.1)	11 (11.6)	7 (7.4)	
Aripiprazole	0 (0)	5 (5.2)	1 (1.1)	

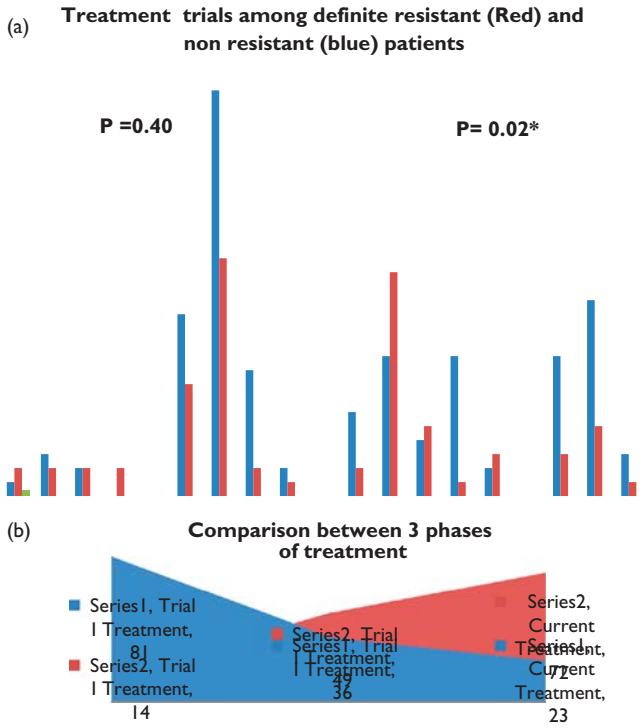
Highly significant if $P<0.001$.

In terms of the history of treatment, the patients had been subjected to two previous trials of a full therapeutic dosage of at least 1000 mg of chlorpromazine for at least 3–6 months, with no satisfactory response. There was a highly significant shift in the treatment characteristics between the two previous treatment trials and the current trial towards the use of atypical antipsychotics ($P = 0.000$; Cochran's test) (Table 3) (Fig. 1a and b), where conventional antipsychotics were used in 85.3% of patients in trial 1, 37.9% in trail 2, and only 24.2% in the current stage. However, the atypical group showed a reverse trend (14.7, 51.5, and 75.7%, respectively). Clozapine and risperidone were among the most frequently prescribed atypical drugs.

The mean current age of the studied sample was 48.9 ± 10.3 years, the mean age at onset of schizophrenia was 21.2 ± 5.7, the mean duration of illness was 27.5 ± 9.3 years, the mean number of relapses was 19.07 ± 12.5 times, and the mean relapse duration was 3.3 ± 3.9 months. They had a chronic continuous institutionalization period of 9.8 ± 6.2 years, and the mean duration of hospital stay was 14.6 ± 7.4 years (Table 4).

Psychometric study indicated that the mean scores of positive, negative, and general psychopathology subscales of PANSS were 17.8 ± 7.0, 28.4 ± 10.9, and 38.15 ± 9.4, respectively; the mean MMSE score was 19.49 ± 7.1 and 5.3 ± 1.1 for the CGIS (Table 4).

Figure 1



(a) Comparison between definite resistant ($n = 36$) and nonresistant ($n = 59$) schizophrenic groups according to their treatment history. (b) Comparison between categories and differential types of antipsychotics used in 95 patients with chronic schizophrenia through three phases of treatment ($P = 0.00$).

Difference between the resistant and the nonresistant schizophrenia group

The results showed no significant difference between the resistant and the nonresistant schizophrenia groups in terms of the sociodemographic or medical characteristics, medical comorbidities, anthropometric measures, treatment history as well as the MMSE score.

Risperidone failure in trial II was significant in resistant patients ($n = 16$), whereas sulpiride ($n = 14$) and trifluoperazine ($n = 10$) were among the most commonly prescribed medications used for nonresistant patients ($P = 0.02$) Fig. 1b.

The only significant difference between the two groups was in the PANSS scores; resistant patients had significantly higher scores ($P < 0.000$) compared with nonresistant patients (Table 4).

In terms of the CGIS score, all resistant patients were significantly moderately to extremely ill (≥ 4), whereas the nonresistant group showed a reasonable distribution (13 cases) in scores (< 4) ($P = 0.03$) (Fig. 2).

Difference between clozapine-resistant schizophrenia, non-clozapine-resistant, and nonresistant groups

Treatment-resistant patients were further divided into clozapine-resistant ($n = 17$) and non-clozapine-resistant ($n = 19$) patients.

There was no significant difference between the clozapine-resistant schizophrenic group, non-clozapine-resistant cases as well as nonresistant cases, in terms of the sociodemographics, clinical characteristics, medical state (Tables 5–7), CGIS (Fig. 3) as well as treatment history (Fig. 4).

In terms of the other psychometric scales, clozapine-resistant patients had significantly higher PANSS scores in all the three subscales compared with the nonresistant and non-clozapine-resistant patients ($P = 0.00$; Fig. 5). However, the mean MMSE scores ($P = 0.34$) did not differ significantly between the three groups: 17.1 ± 7.7; 20.0 ± 6.8; and 20.0 ± 7.7, respectively.

Using the logistic regression model (χ^2 model = 11.807, significance = 0.05, $R^2 = 0.159$) (Table 8), it was found that young age (< 40 years) and early onset of schizophrenia (< 20 years) were powerful predictors for schizophrenia resistance. Other factors of sociodemographics and psychopathological severity lacked this predictive value.

Discussion

Prevalence of treatment-resistant schizophrenia

In the current study, 37.8% of patients with chronic schizophrenia had resistant schizophrenia according to the modified Kane *et al.*'s (1988) criteria.

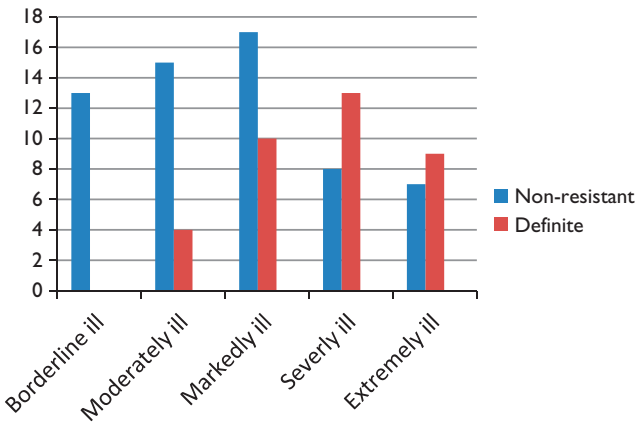
The prevalence in the current study is concomitant with the range of resistant schizophrenia and treatment nonresponse cases in other studies. The range of nonresponsiveness was reported to be 20–30% and up

Table 4 Comparison between definite resistant ($n=36$) and nonresistant ($n=59$) schizophrenic cases according to age and clinical data

	Mean ± SD		
Item	Nonresistant	Resistant	*P*-value
Age	49.9 ± 9.8	46.6 ± 10.9	0.12
Age at onset	21.8 ± 5.2	20.2 ± 6.3	0.19
Duration of illness (years)	28.05 ± 9.6	26.6 ± 8.9	0.48
Relapse number	19.5 ± 13.5	18.2 ± 10.8	0.63
Relapse duration (months)	3.8 ± 4.8	2.6 ± 1.4	0.12
Last duration stay in hospital (years)	10.07 ± 5.7	9.4 ± 7.02	0.63
Total stay duration in hospital (years)	15.3 ± 7.2	13.6 ± 7.8	0.30
MMSE	20.1 ± 6.7	18.3 ± 7.7	0.24
PANSS positive subscale score	14.1 ± 4.8	22.01 ± 2.51	0.000*
PANSS positive subscale score	27.5 ± 6.3	33.6 ± 7.59	0.000*
PANSS psychopathology score	34.01 ± 7.1	45.01 ± 8.2	0.000*

MMSC, Mini-mental State Examination; PANSS, Positive and Negative Syndrome Scale.
Significant if $P<0.05$.
*Highly significant if $P<0.001$.

Figure 2



Severity of illness of definite resistant ($n=36$) and nonresistant ($n=59$) schizophrenic patients according to the Clinical Global Impression Severity scale.

to 60% cases were not responding to conventional antipsychotics (Itil *et al*., 1966; Kane *et al*., 1988; Meltzer and Kostacoglu, 2001; Miller *et al*., 2006).

This wide range of schizophrenia nonresponders may be because of methodological differences and definition defendant (Juarez-Reyes *et al*., 1995; Essock *et al*.,1996; Solanki *et al*., 2007). The large percentages reported by some investigators may have been because they did not differentiate cases with true resistance from those who had only received inadequate treatment, especially in terms of the dosage, compliance, and duration (Elkis and Meltzer, 2007), or may have used more restricted and less broad diagnostic criteria as in the study of Juarez-Reyes *et al*. (1995), who applied the American Psychiatric Association 1980 criteria, with a mean prevalence 42.9 ± 5.9%, and this estimate reduced to 12.9 ± 2.7% when the Kane *et al*.'s criteria were used, which are more restrictive. These estimates of the prevalence of

Table 5 Sociodemographic data of clozapine-resistant ($n=17$), non-clozapine-resistant ($n=19$), and nonresistant ($n=59$) patients with schizophrenia

Item	Nonresistant ($n=59$)	Non-clozapine resistant ($n=19$)	Clozapine resistant ($n=19$)	Total ($n=95$)	Pearson's $\chi^2(3)$ LLR $\chi^2(3)$
Sex					
Female	10	3	2	15	0.66
Male	49	16	15	80	
Marital status					
Single	38	15	14	67	0.494
Married	9	1	2	12	
Divorced	10	2	1	13	
Widowed	2	1	0	3	
Job history					
Jobless	40	14	14	68	0.67
Professional	1	1	0	2	
Retired	18	4	3	25	
Education					
Illiterate	15	5	1	21	0.3
Low grade	32	9	12	53	
High grade	11	4	2	17	
University	1	0	2	3	

LLR, log-likelihood ratio.
Highly significant if $P<0.001$.
Significant if $P<0.05$.

Table 6 Clinical characteristics of clozapine-resistant ($n=17$), non-clozapine-resistant ($n=19$), and nonresistant ($n=59$) patients with schizophrenia

Item	Nonresistant ($n=59$)	Non-clozapine resistant ($n=19$)	Clozapine resistant ($n=17$)	Total ($n=95$)	Pearson's χ^2 (3) LLR χ^2 (3)
Schizophrenia subtypes					
Undifferentiated	27	9	5	41	0.12
Paranoid	11	3	8	22	
Residual	11	2	1	14	
Disorganized	4	3	3	10	
Schizoaffective	5	2	0	7	
Symptom at onset					
Negative	3	0	0	3	0.55
Positive	43	15	14	71	
Mixed	13	4	3	20	
Family history of medical illness					
Positive	17	12	11	40	0.65
Negative	42	7	6	55	
Family history of psychiatric illness					
Positive	29	10	9	48	0.97
Negative	30	9	8	47	
Diabetes mellitus					
Positive	18	5	9	28	0.74
Negative	41	14	8	67	
Hypertension					
Positive	21	4	5	30	0.32
Negative	38	15	12	65	
Dyslipidemia					
Positive	31	9	7	47	0.69
Negative	28	10	10	48	

LLR, log-likelihood ratio.
Highly significant if $P<0.001$.
Significant if $P<0.05$.

Table 7 Comparison between clozapine-resistant ($n=17$), non-clozapine-resistant ($n=19$), and nonresistant ($n=59$) patients with schizophrenia in terms of age and some important clinical durations related to illness

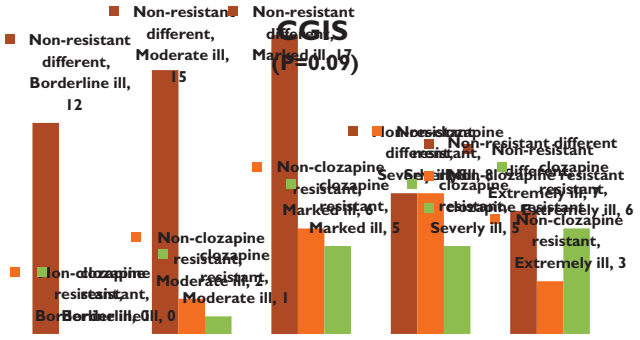
Item	Mean ± SD				
	Nonresistant	Non-clozapine resistant	Clozapine resistant	Total ($n=95$)	*P*
Age	49.9 ± 9.7	48.1 ± 11.2	44.8 ± 10.9	48.7 ± 10.3	0.1
Onset age	21.8 ± 5.1	20.2 ± 4.4	20.1 ± 8.2	21.2 ± 5.7	0.41
Duration of illness (years)	28.03 ± 9.5	28.2 ± 10.1	24.9 ± 7.7	27.5 ± 9.3	0.4
Relapse number	19.4 ± 13.4	20.3 ± 11.4	16.2 ± 10.3	19.0 ± 12.5	0.57
Relapse duration (month)	3.8 ± 4.8	2.6 ± 1.4	2.4 ± 1.5	3.3 ± 3.9	0.32
Last duration stay in hospital (years)	10.1 ± 5.7	8.8 ± 6.9	9.9 ± 7.3	9.8 ± 6.2	0.75
Total stay duration in hospital (years)	15.3 ± 7.1	14.4 ± 8.2	12.7 ± 7.8	14.6 ± 7.4	0.40

Highly significant if $P<0.001$.
Significant if $P<0.05$.

Table 8 Logistic regression model for significant predictors of resistant schizophrenia according to Kane's criteria for 95 patients with schizophrenia

Resistant schizophrenia = 1.701 constant
+ 2.17 of age (years) lower than 40
OR = 8.77 (0.935–82.33)
+ 0.451 age of onset (years) of schizophrenia if before 20
OR = 1–56 (0.614–4.011)
χ^2 model = 11.807
Significance = 0.05
$R^2 = 0.159$

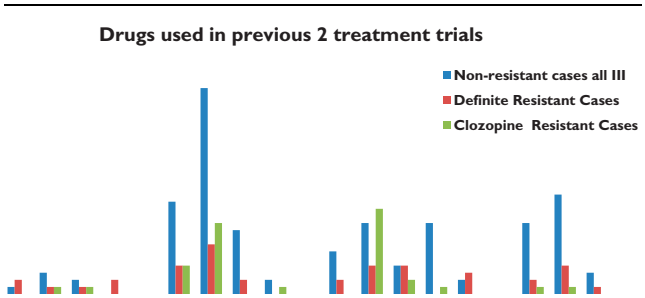
Figure 3



Clinical Global Impression Severity (SGIS) scale scores among clozapine-resistant ($n=17$), non-clozapine-resistant ($n=19$), and non-resistant ($n=59$) patients with schizophrenia.

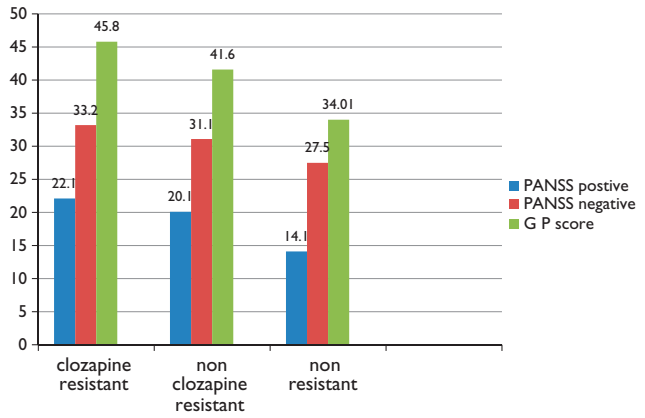
treatment resistance are similar to those when clozapine was first marketed, extrapolating to a total of 2 00 000–5 00 000 patients with TRS currently living in USA (Terkelsen and Grosser, 1990).

Figure 4



Previous nonresponsive treatment trials in clozapine-resistant ($n=17$), non-clozapine-resistant ($n=19$), and nonresistant ($n=59$) patients with schizophrenia.

Figure 5



Mean Positive and Negative Syndrome Scale (PANSS) score for clozapine-resistant ($n=17$), non-clozapine-resistant ($n=19$), and non-resistant ($n=59$) patients with schizophrenia ($P=0.000$) for the three subscales.

Effect of antipsychotics

Since the demonstration of clozapine's superior efficacy, attention has shifted to the use of new antipsychotics for TRS. To obtain approval for marketing in the USA, new antipsychotics must have a safety or an efficacy profile that is superior to conventional neuroleptics.

In the current study, there was a highly significant shift from the use of conventional antipsychotics (85.3-24.2%) to the use atypical group (14.7-75.7%), especially clozapine [$n=37$ (38.9%)]. This is quite logic and expected as the practice of most of psychiatrist was dependant previously on the use of traditional drugs based on their availability and cost as well as the claim of equal efficacy compared with second-generation drugs. Most studies have concluded that there are no apparent consistent differences between antipsychotic agents with respect to their effect, but only in their tolerability and adverse effect profile (Geddes *et al.*, 2000; Keefe *et al.*, 2007; Davidson *et al.*, 2009; Hill *et al.*, 2010) or dropout rates (CATI study phase 1; Keefe *et al.*, 2003).

The shift to newer agents, especially clozapine, is relevant and has been documented in open and controlled studies because of the superior effect of clozapine on positive and negative symptoms compared with previous treatment with typical (Pickar *et al.*, 1992; Meltzer, 1997; Lehman *et al.*, 2004a, 2004b; Miller *et al.*, 2004) and even new atypical antipsychotics with twice effect size (0.44) than later one (0.29) (Davis *et al.*, 2003; Stroup *et al.*, 2003; Solanki *et al.*, 2007; CATI study phase II; Lieberman *et al.*, 2005; Lewis *et al.*, 2006; Keefe *et al.*, 2007 McEvoy *et al.*, 2006).

There was no significant difference between resistant and nonresistant patients with schizophrenia in the treatment profile in the current study, except that resistant patients failed to respond to risperidone significantly more than nonresistant patients in trial II of treatment. This in general may indicate that some atypical antipsychotics are less effective, with a higher failure rate, in the treatment of schizophrenia resistance.

In some studies, risperidone has shown a lower efficacy profile (Chouinard *et al.*, 1994; Cohen and Underwood, 1994; Cardoni, 1995; Keck *et al.*, 1995; Klieser *et al.*, 1995). However, reports on the effectiveness of risperidone, which was comparable with other second-generation agents including clozapine and first-generation agents including haloperidol (Smith *et al.*, 1996; Bondolfi *et al.*, 1998; Wirshing *et al.*, 1999), are in agreement with our results. This may support the hypothesis that the response to treatment may be varied depending on several factors including the biological makeup of patients, especially those with resistant schizophrenia.

Even with clozapine, 30% of patients are labeled ultraresistant, with a poor response to clozapine (Buckley *et al.*, 2001; Chakos *et al.*, 2001), indicating the inconsistency of the efficacy of antipsychotics and may be the biological basis for treatment response, especially in resistant or ultra resistant schizophrenic patients.

Predictors of treatment resistance

Younger age (<40 years) and early age at onset (<20 years) were powerful predictors of treatment resistance in our sample. These results were in agreement with those of Meltzer (1992), indicating that resistance and poor outcome are linked to younger age at onset (<20).

The lack of a significant association between schizophrenia resistance and the sociodemographics, clinical profile, treatment history, and medical state may indicate the presence of multiple factors behind resistance including intrinsic biological factors of the individual, psychological and behavioral characteristics, pharmacogenetic, biological comorbidities, family factor, social, and personal and noncompliance predispositions.

Some studies have indicated intrinsic biological factors such as ventricular enlargement and cortical atrophy predominance in resistant cases as well as low plasma homovanillic acid and alternatives of function and concentration of T cells and some interleukins (Lieberman *et al.*, 1996; Elkis and Meltzer, 2007). Mouaffak *et al.* (2011) found that genetic factors have a significant association with ultraresistant schizophrenia.

In addition, Xiu *et al.* (2009) have reported lower levels of brain-derived neurotrophic factors in chronic patients with schizophrenia than in healthy control individuals, and this was observed in patients treated with risperidone (9.3 ± 2.3 mg/ml) compared with those treated with clozapine (10.2 ± 2.0 mg/ml, $P<0.001$) and atypical antipsychotics (10.0 ± 2.1 mg/ml, $P<0.01$).

In summary: research studies on TRS can be the basis for the identification of a subgroup of schizophrenia patients, who have a unique etiology, possibly on genetic basis or gene–environment interactions. This may not only lead to the development of effective treatments for these individuals but may also reduce hetrogenicity and allow the study of the etiology of schizophrenia in those who respond adequately to current medications.

Conclusion and recommendations

(1) Treatment resistance-schizophrenia is quite common, especially among chronic patients.
(2) Some clinical factors such as younger age and early onset age of schizophrenia are predictors for non-responsiveness.
(3) Focusing on intrinsic biological factors of illness and individuals through pharmacogenetic studies can aid the detection of the risk of schizophrenia resistance, poor response to treatment, and poor outcome.
(4) More studies for valuable, clinical guidelines as well as algorithms for treatment-resistant cases with recommended aggressive treatments of first-episode schizophrenia may eliminate subgroups of cases with suspected refractoriness.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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