

CLOZAPINE IN TREATMENT OF SCHIZOPHRENIA

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Abstract: *The introduction of clozapine for the treatment of non responsive patients with schizophrenia has determined a real hope among patients, families and psychiatrists. This treatment is available that appears to be more effective than the standard or typical neuroleptics for many such treatment-resistant schizophrenic patients. A growing number of reports suggest that clozapine may also have a role in other psychiatric conditions such as manic episode. Even though this review will focus on treatment-resistant positive symptoms, there is good evidence that psychosocial treatments, such as vocational rehabilitation and social skills training, can contribute to recovery of function once the debilitating psychotic, or positive, symptoms are adequately treated.*

The data from our study add to the growing evidence for efficacy of clozapine in schizophrenia.

Key words: *schizophrenia, clozapine, antipsychotics.*

1. Introduction

Clozapine is the only drug specifically indicated for treatment-resistant schizophrenia and also for treatment of patients with high risk of suicide and aggressive behavior. A meta-analysis of randomized clinical trials confirmed its superiority in this patient population compared with other antipsychotics, both first- and second-generation [1].

Certain serious clinical conditions in schizophrenia are particularly responsive to clozapine, including persistent auditory hallucinations, persistent hostility, suicide risk, and tardive dyskinesia [2].

Drawbacks include the complications of weekly venipuncture during the first 6 months of treatment, then biweekly thereafter, to monitor for agranulocytosis, which affects 1% of patients. Other adverse effects include seizures, myocarditis, weight gain, and hyperglycemia, as well as early mortality from cardiovascular disease [3].

Despite these, patients with schizophrenia taking clozapine may have better adherence to treatment than other patients because of improved functional status and more frequent contact with providers. A growing number of reports suggest that clozapine may also have a role

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in other psychiatric conditions such as manic episode [4]

Some patients, however, do not have an adequate response to clozapine. As with other medications, adherence and pharmacokinetic matters must be addressed.

2. Method

This project was a 24-months non-interventional and observational study from January 2009 to December 2010, conducted in Clinical Department for acute patients belonging to the Psychiatry and Neurology Hospital, the most important in the region. Patients with age above 18 years were considered for entry into the study if they were eligible according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as having schizophrenia in acute exacerbation.

Our study was designed to investigate the treatment management of a really heterogeneous patients with schizophrenia hospitalized for acute exacerbation in a naturalistic setting of acute psychiatric departments and to identify the patterns of treatment used by the psychiatrist when they decided to use clozapine.

Investigators recorded all the data about the patients (gender, age, age of onset of schizophrenia, marital status, education, type of assurance, number of days of hospitalization) and data regarding pharmacotherapy that had been prescribed during hospitalization.

Patient's demographics and illness characteristics were analyzed using descriptive statistics. We used Analysis of variance (ANOVA) including post-hoc comparisons to test the difference between means in first generation antipsychotics (FGA) and second generation

antipsychotics (SGA) groups. Categorical data were analyzed using Chi-square test. All calculations were made by Stat Soft Statistics v.4.5. Statistical significance was set at *P* value less than 0.05.

3. Results

A total of 273 patients hospitalized for an acute exacerbation of schizophrenia entered into the study.

The vast majority of patients met the criteria for paranoid schizophrenia (74.8%), followed by undifferentiated schizophrenia (21.3%), disorganized schizophrenia (1.2%) and catatonic type (0.08%).

The mean age across the group was 42.67 years (SD=11.2) with significant difference between female and male (female mean age was 44.25 and male mean age was 41.1, $p < 0.001$).

It was also a difference between female and male regarding the age of onset of schizophrenia; the mean age of onset of schizophrenia in male was with 2.9 years earlier than in female cases (25.63 vs.28.52, $p < 0.001$).

The mean schizophrenia duration was 15.72 years (SD=9.4), being higher in women than men (16.91 vs.14.54).

The level of education of the group was relatively high, with mean years of education above 10 years of studies, greater in male cases.

The results of hospitalization indicated a mean of 22.25 days (SD=10.50), almost equal for female and male.

The mean age of onset of schizophrenia was statistically significant lower in male patients treated with SGAs compared with those treated with FGAs (24.62 vs. 26.84, $p < 0.001$).

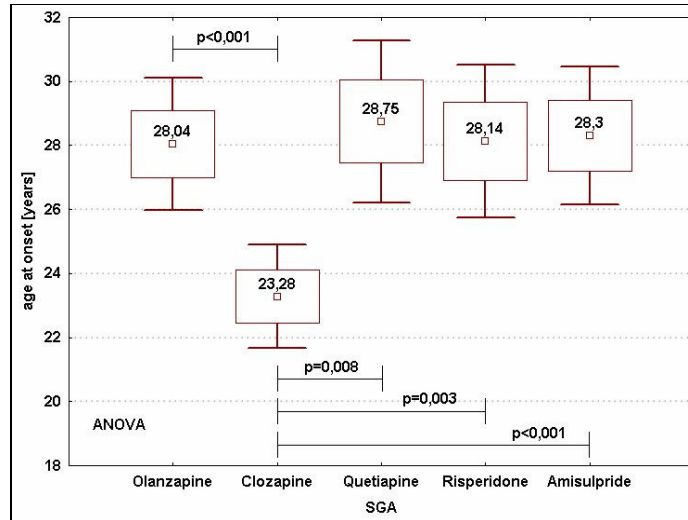


Fig. 1. Age of onset of schizophrenia and antipsychotic treatment

An important aspect of our study was to evaluate the combinations used in treatment of schizophrenia indicated at discharge after an acute episode.

All patients with schizophrenia under study were treated with first or second generation antipsychotics in different

proportions. Of 273 patients treated with „atypical” received amisulpride (25.27%), aripiprazole (0.7%), clozapine (26.37%), olanzapine (27.73%), quetiapine (7.32%) and risperidone (13.55%).

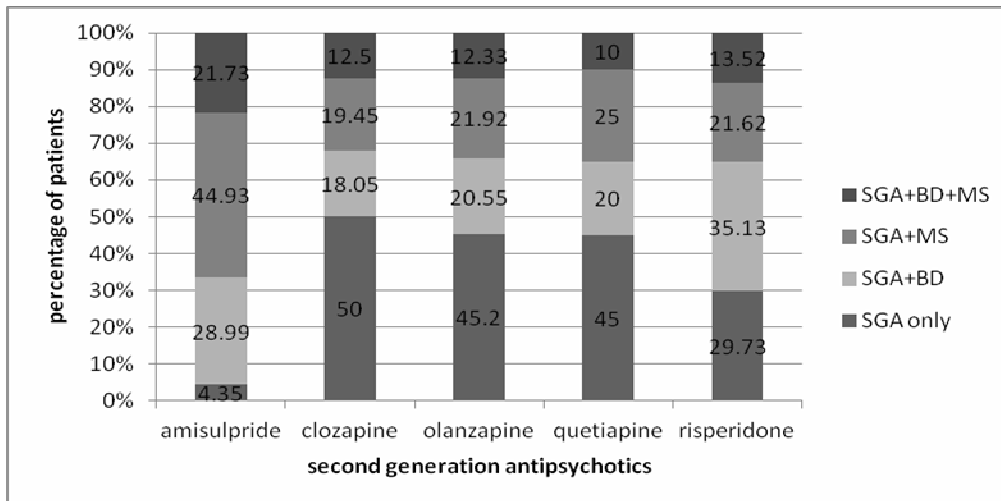


Fig. 2. The most used antipsychotics in treatment of schizophrenia

There were only 14 patients who received FGAs alone at discharge (6.70%) compared with 93 patients who received mono-therapy with SGAs (34.06%, $p < 0.0001$).

Combination between FGAs and benzodiazepine was indicated in 11.00% of cases being lower than in SGAs and benzodiazepine with was prescribed in 19.41% of cases ($p = 0.01$). The number of patients who received anti-parkinsonian compounds in combination with antipsychotics was significantly higher for FGA ($p = 0.0004$).

The combination antipsychotic-benzodiazepine-mood stabilizer triple combination was found in approximately equal proportions for the two types of antipsychotics ($p = 0.69$).

The number of patients who have had their treatment regimen at discharge with a combination included antipsychotic-benzodiazepine-mood stabilizer and anti-parkinsonian was significantly greater in FGAs cases (16.27%) compared with SGAs (2.93%), $p < 0.0006$. Analysis of variance between the type of treatment chosen at discharge and the average length of hospitalization revealed no statistically significant differences between the group treated with FGAs and SGAs, the values obtained were approximately equal.

It was a significant difference between atypical antipsychotics in terms of psychotropic added; amisulpride was prescribed alone in 4.35% cases and was associated most frequently with benzodiazepine, mood stabilizers or both of them compared with olanzapine and clozapine ($p < 0.005$).

The treatment with clozapine alone was recorded in 50%. We observed many similarities between treatment with clozapine and olanzapine (the almost same percentage regarding number of patients treated with those antipsychotics and the number of patients who needed benzodiazepine and mood stabilizers).

There were no significant differences regarding hospitalization, gender and type of antipsychotic treatment between the two groups.

The mean duration of illness was greater in group treated with FGAs compared with SGAs group and it was significant for male ($p < 0.001$).

5. Discussions

Some patients with chronic psychotic disorders have mood symptoms or cycling, and because GABA modulates dopamine activity in the central nervous system, clinicians may consider valproate to augment an antipsychotic. A review showed that valproic acid added to haloperidol, olanzapine, or risperidone found no significant reduction in overall psychopathology compared with placebo in trials of ≤ 12 weeks' duration [5]. The subjects in the trials had schizophrenia or schizoaffective disorder but were not necessarily treatment resistant. Two studies, however, have documented a specific improvement in hostility among patients with schizophrenia taking haloperidol, olanzapine, or risperidone and adjunctive valproic acid, an important finding requiring further research [6-8].

Table 1
Types of atypical antipsychotics

Atypical antipsychotics	Mono-therapy	
	N	%
amisulpride n=69	3	4.35
clozapine n=72	36	50
olanzapine n=73	33	45.23
quetiapine n=20	9	45
risperidone n=37	11	29.72
TOTAL	92	34.86

6. Conclusions

Our observational study was the first study in Romania who intended to explore the patterns in antipsychotic treatment with clozapine in patients with schizophrenia in terms of demographics, hospitalization duration and necessity of other psychotropic compounds.

Despite treatment guidelines and consensus of experts in psychiatry, the severity of schizophrenia frequently required adaptation of treatment and therapeutic combinations that often exceed imposed boundaries [9, 10].

In our study we noted the high percentage of patients who received treatment with clozapine, often in attempting to resolve psychotic symptoms or extreme agitation.

Although all antipsychotics have been used in therapeutic doses, most times the maximum recommended dose, lack of therapeutic response in many cases required a combination of a benzodiazepine or mood stabilizer even in a clozapine case.

The challenge of treatment-resistant schizophrenia with agitation or high risk of aggressive behavior continues despite the advent of a second-generation class of antipsychotics. The increased off-label use of combination therapies of 2, 3, or even 4 drugs, is an indication that many clinicians still encounter a substantial number of patients who do not adequately respond to the approved doses of antipsychotic medications [11].

Further research in treatment of schizophrenia is clearly needed to address the needs of patients who remain substantially symptomatic and disabled even with the use of currently available antipsychotic agents [12].

In Romania, psychiatrists exhibited different approach of clinical concepts and

on prescription guidelines of antipsychotics and they are influenced by patient's age and personal experience [13].

It is necessary to reach a consensus to establish and standardize the treatment of schizophrenia, based on the information reported in naturalistic trials to avoid inadequate treatments in schizophrenia.

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