Research article
Ερευνητική εργασία

Evaluation of therapy with clozapine in outpatient treatment-resistant schizophrenics in Cyprus

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Clozapine is an atypical antipsychotic formulation indicated for schizophrenic patients who are unresponsive or intolerant to traditional antipsychotic therapy. Treatment with this agent is prevalent among schizophrenic patients under psychiatric hospital care, but not among non-hospitalized patients. The aim of this study was to evaluate the response to clozapine treatment, and specifically the effects on the overall functioning of a group of out-patient treatment-resistant schizophrenics. Data from 66 treatment-resistant schizophrenics in Cyprus, 28 female and 38 male, were retrospectively retrieved. The scales used for assessment were Global Assessment of Functioning Scale (GAF) and the Positive and Negative Syndrome Scale (PANSS). Also, white blood cell (WBC) counts were examined. Based on the GAF scale it was determined that there was a 49.7±23.6 SD point ($P<0.001$) significant improvement in the functioning of these patients at the end of the evaluation period with clozapine. Furthermore, utilizing the PANSS, it was concluded that treatment with clozapine significantly improved the positive and negative symptoms as well as the general psychopathology of this patient group. In total, 9 patients were taken off the medication because 2 patients (3%) were completely cured, 5 patients (8%) were unresponsive, 2 (3%) were non-compliant, 1 (2%) developed diabetes and 1 (2%) had considerably low WBC counts during the treatment. The incidence of WBC reduction and need for discontinuation of therapy falls within the expected range of this abnormality in patients taking clozapine. WBC counts were performed weekly for the first 18 weeks and monthly thereafter showed that there was no negative effect on the WBC counts of 65 out of the 66 patients, and thus indicate that clozapine can be safely administered at an out-patient basis. The data indicate a strong improvement in the functioning of this group of patients under outpatient clozapine treatment, without compromising patient safety.

Key words: Schizophrenia, antipsychotic treatment, out patients clozapine, functioning, GAF (Global Assesment Functioning), Scale, PANSS (Positive and Negative Symptoms) Scale.

Introduction

Schizophrenia is a chronic, debilitating psychotic mental disorder that affects about 1 percent of the population. Schizophrenia is an illness or a group of illnesses affecting language, planning, emotions, perceptions and movements. Many divide its signs and symptoms into "positive" and "negative". Common positive symptoms are delusions, hallucinations, disordered thinking and catatonic movements. Negative symptoms refer to the absence of function (emotional numbness, social withdrawal, lack of motivation, apathy). The effectiveness of antipsychotic medications used for the treatment of schizophrenia reduce the intensity of patients' delusions, hallucinations and other symptoms and permitted outpatient treatment instead of lifelong institutionalization in state mental hospitals. Clozapine is the prototype atypical agent indicated for the treatment of schizophrenia failed to respond to other antipsychotic medications, while no other drug has been approved by any competent authority for this indication. Clozapine proved to have enhanced therapeutic efficacy as compared with the first generation drugs[1] but also compared to other antipsychotic medications belonging to the so called group of atypical antipsychotics. Treatment resistant schizophrenia is defined by an inadequate response or the patient failing to return to its premorbid condition, following the administration of at least two different antipsychotic medications at adequate doses for a period of at least six months. The efficacy of clozapine in patient with treatment refractory schizophrenia was established in the NIMH multicentre study.[1] Clozapine indeed proved to be more effective at reducing symptoms than other neuroleptic agents. This relapsing illness often necessitates hospitalization and additional long term care even in periods the patient does not need to be hospitalized. While hospitalization relieves families from the burden of providing proper care to their members, in small countries this becomes many times a social stigma. It is a medical challenge to keep patients within the family environment, while providing an effective pharmacological treatment and quality of life both for the patient and his/her family. Studies of treatment with clozapine of seriously ill population found a significant reduction in readmissions, hospitalization days and emergency room visits.[2,3]

Outpatient treatment is an accepted option if it is in the service of reducing the risk of re-hospitalization. It does appear that outpatient treatment with clozapine is a viable option to consider, particularly with patients where hospitalization is not an option for any reason and for patients who despite some improvement with the use of other antipsychotic medication have not returned to their premorbid condition. However, as the drug carries about a 1% risk of potentially fatal agranulocytosis, blood monitoring is part of the prescribing process and may demand for a well controlled environment for proper blood monitoring to be implemented. Having all these in mind we had decided to introduce clozapine as a standard treatment to all our outpatients that were remaining symptomatic despite adequate treatment with other antipsychotic agents.

Material and method

Study design and sample

This was an observational, retrospective, chart review study. Data were retrieved from the charts of 66 treatment-resistant schizophrenics, who met the DSM-IV criteria for schizophrenia, in Cyprus, 28 female and 38 male. This data included, in addition to the gender, the age, the marital and the occupational status of these patients. We also had data on the age of first treatment with clozapine (Leponex®, Novartis), the duration of clozapine treatment, the maximum dose of clozapine and the combination therapy with other antipsychotic drugs. We retrieved the data regarding safety of clozapine from patient's chart review. All patients signed informed consent forms and the study was conducted under the ICH-GCP guidelines and the Declaration of Helsinki.

Methodology and tools

The aim of this study was to evaluate the response to clozapine treatment, and specifically its effects on the overall functioning of a group of 66 outpatient

treatment-resistant schizophrenics. For that we assessed the change in patients' marital and employment status at the initiation and at the end of treatment with clozapine. For the current study treatment-resistance was defined as inadequate or no response to previous therapy with common antipsychotic drugs.

In order to determine whether clozapine treatment improves patient function, the Global Assessment Functioning Scale (GAF scale) was used. The GAF scale is a numeric scale (0 through 100) used by mental health clinicians and doctors to rate the social, occupational and psychological functioning of adults. The scale is presented and described in the DSM-IV. In this study the GAF scale was measured before the application of Leporex and after the end of the observational study.

In order to determine whether clozapine treatment improves positive and negative symptoms of schizophrenia the Positive and Negative Syndrome Scale (PANSS) was used. The PANSS is a medical scale used for measuring symptom reduction of schizophrenia patients. The scale has seven positive-symptom items, seven negative-symptom items, and 16 general psychopathology symptom items. Each item is scored on the same seven-point severity scale. The 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. Based on two established psychiatric rating systems, it thus constitutes four scales measuring positive and negative syndromes, their differential and general severity of illness. For the PANSS scale 20 patients were randomly selected from this observation group of 66 treatment- resistant schizophrenics. For the patients' positive and negative symptoms, as well as general psychopathology, the 20 patients were assessed at baseline and at the end of the observational period.

According to the literature, the risk of agranulocytosis appears to be higher in the first 3 months of treatment, increases with age and appears to be higher in women. Consequently patients in this study had weekly complete blood count (WBC) testing for the first 18 weeks and then monthly, also at the beginning of their clozapine treatment and at their last visit. The WBC count must be maintained at or above 3000/mm^3, and the absolute neutrophil count must be maintained at or above 1500/mm^3. Patients with a significant decrease in WBC count will be withdrawn from the medication.

Statistical analysis

Descriptive statistics are presented as in mean ±SD whereas categorized variables are summarized in frequency distribution tables. The alteration of GAF and PANSS scale from baseline to the end of observation period is assessed by paired samples t-test. All tests were 2-sided and level of statistical significance was set at 5%.

Results

66 outpatient schizophrenics with 29.4±9.5 mean years of age and 6.2±4.3 years of clozapine treatment were evaluated. Out of the 66 patients 64 were Greek- Cypriots one was a Turkish-Cypriot and one had an Armenian ethnic origin. 49 out of 66 patients (74.2%) received clozapine as monotherapy. 16 patients (24.3%) received risperidone as concomitant medication in variant doses. 1 patient (1.5%) received risperidone and hydrochloride trifluoperazine as concomitant medication (table 1).

Table 1. The baseline demographic characteristics of the patients.

Patients	
Male	38
Female	28
Mean age on starting clozapine treatment	29,4 ± 9,5 years
Mean period on clozapine treatment	6,2 ± 4,3 years
No of patients on clozapine monotherapy	49 (74,2%)
No of patients taking additional medications	22 (25,8%)

This study was designed to assess the efficacy and safety of clozapine (Leponex®, Novartis) administered in escalating doses in adults with treatment-resistant schizophrenia. The starting dose of clozapine was 25 mg three times a day and doses were gradually increased until the maximum tolerable dose, which also yielded the maximum results. The highest dose achieved was 800 mg, for one patient, and the lowest dose was 300 mg, for two patients. 22 patients received 500 mg of clozapine for their treatment, 17 patients received 400 mg of clozapine and 14 patients 600 mg of the drug (figure 1). The marital and employment status of all 66 patients were recorded at baseline (prior to initiation of the drug) and at the end of the observational period. Before drug administration 56 patients were single, 9 were married and 1 was divorced. At the end of the study 50 patients were single, 13 were married/engaged, 2 were divorced and 1 became a widow/er with two children (figure 2). Due to the small number of our patients we didn't performed a specific analysis on the marital status but there is evidence that they were able to establish relations with a partner of the opposite sex and to enrich the quality of their life. The same with marital status applies for the employment status of our patients. At baseline 33 patients were employed, 21 unemployed and 12 were students. At the end of the observational period 37 patients were employed, 23 unemployed and 6 were students (figure 3).

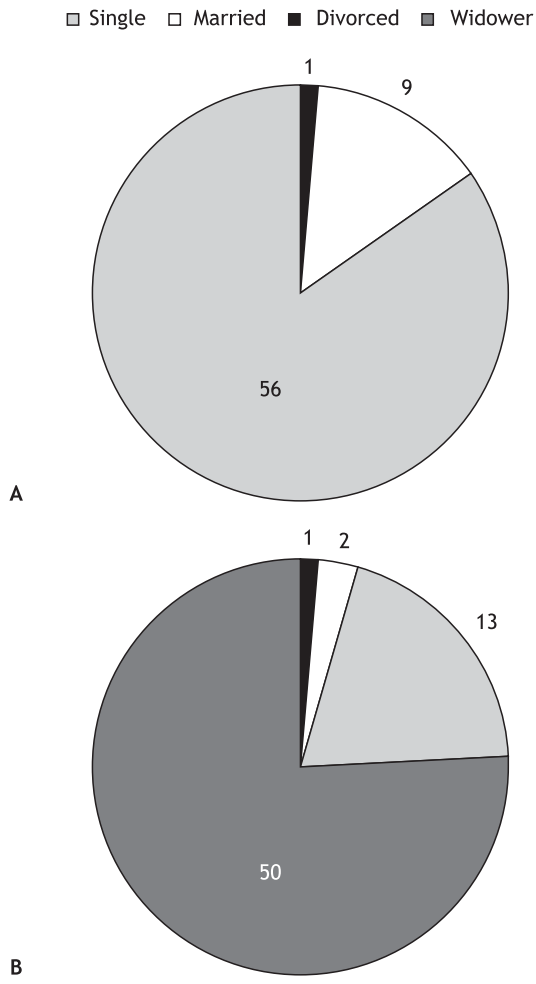

Figure 2. Marital status of patients before treatment with clozapine and at the end of observation period. (A) The marital status of the 66 patients at baseline. (B) The marital status of the patients at the end of the observational period.

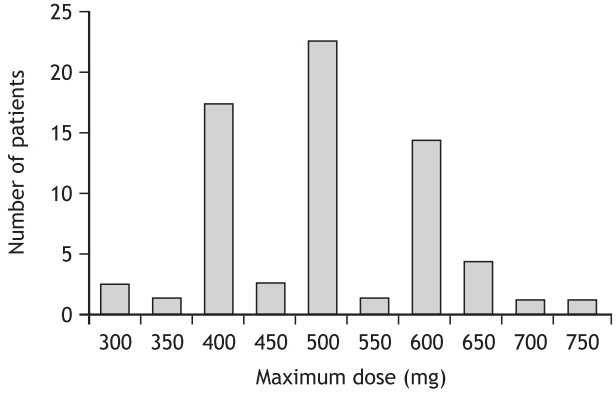

Figure 1. Maximum dose distribution for the patient population. Patients were treated with increasing doses of clozapine, until the optimum maximum tolerated dose for each patient was achieved.

By the end of the observational period, 4 out of the 12 patients that were students at baseline were successfully employed, 4 were still college students, 2 changed to university students and 2 finished their studies but were not able to be employed at the end of the observation period (figure 4). Again here, and despite without proper statistical analysis of this patients population, it seems they have been able to finish their studies and to be successfully employed.

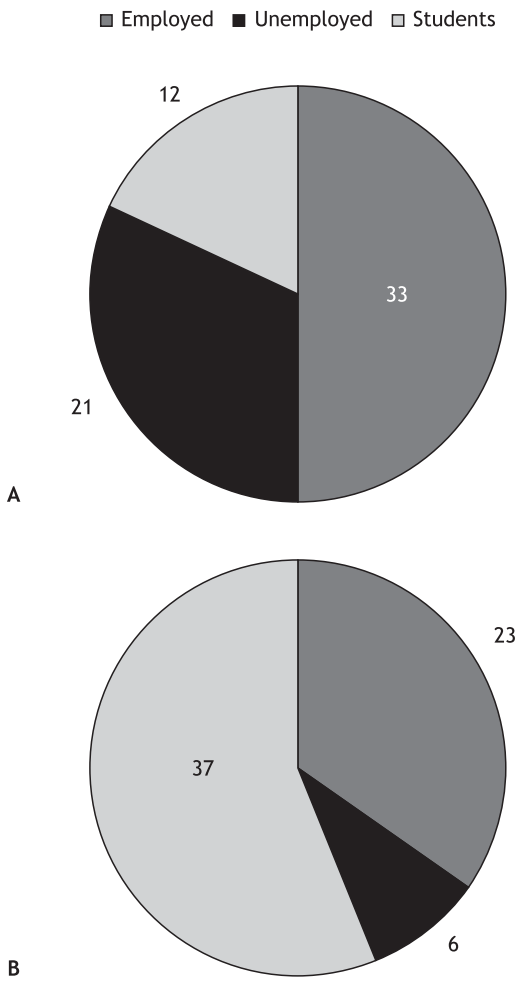

Figure 3. Employment status of patient changes after treatment with clozapine. (a) The employment status at baseline. (b) The employment status at the end of the observational period.

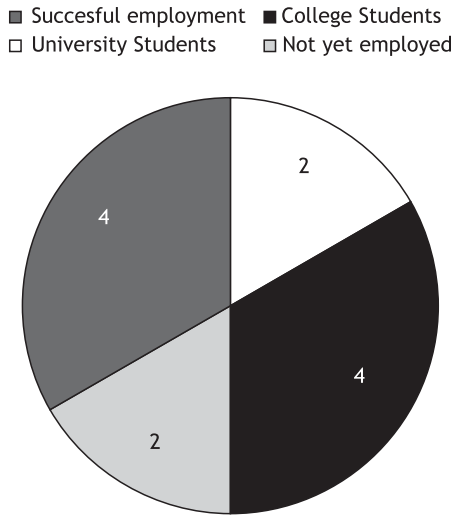

Figure 4. The changes in the employment status of the 12 patients who at baseline were students.

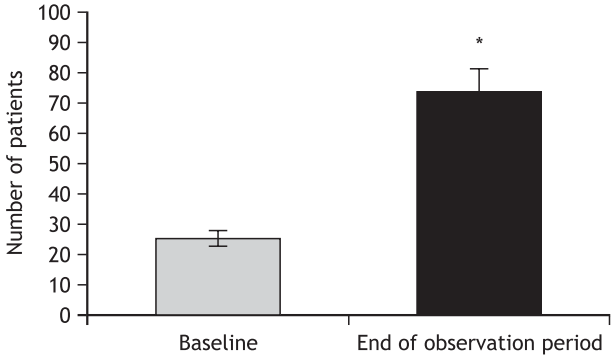

Figure 5. Change in GAF values. GAF values were recorded for all 66 patients at baseline (prior to initiation of treatment with clozapine) and at the end of the observation period. Bars stand for the 95% CI of the means, P≤0.05.

GAF values for each patient were given at baseline and at the end of the observational period. Based on the GAF scale it was determined that there was a significant improvement of 49.7±23.6 points (P<0.0001) on the GAF scale for the 66 patients (figure 5). To further evaluate the overall response of these schizophrenic patients to clozapine treatment, and for 20 patients we had relevant records at baseline and at the end of the observational period an additional analysis was performed. The patients' positive and negative symptoms, as well as general psychopathology were assessed. Clozapine treatment improved the PANSS scale of these patients by 20.9±3.85 points (P<0.0001) (figure 6). A decrease of 37.8±4.10 points (P<0.0001) in general psychopathology of the 20 randomly selected patients was observed at the end of the observational period (figure 7).

During the study WBC cells were monitored for any discrepancies. 65 out of the 66 patients showed

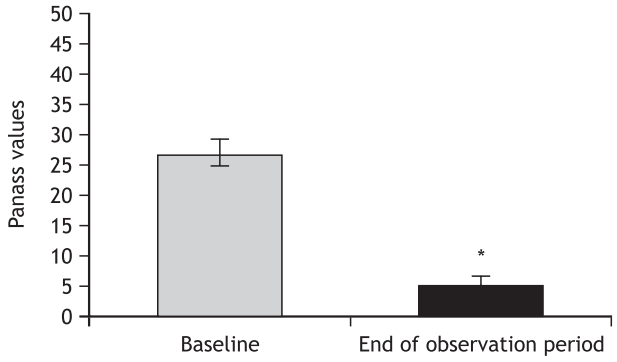

Figure 6. Change in PANSS Scale (positive symptoms) in 20 patients where relevant information were available and treated with clozapin. Bars stand for the 95% CI of the means, P≤0.05.

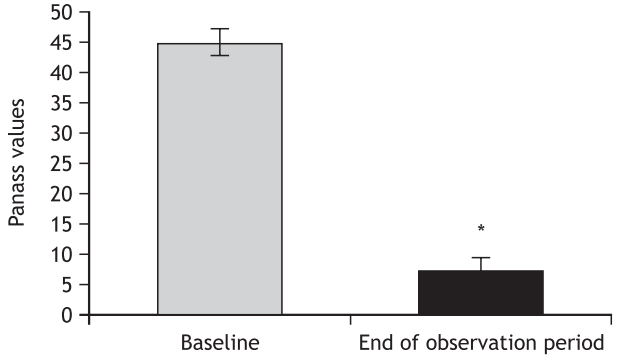

Figure 7. Change in PANSS Scale (general psychopathology scale) in 20 patients where relevant information were available and treated with clozapine.

normal WBC levels throughout the treatment. One patient developed low WBC 10 months after treatment initiation and went off study. WBC returned to normal 42 days after the patient discontinued clozapine. Also serum glucose was monitored and was found that one patient developed diabetes mellitus during treatment, so treatment was terminated. The patient recovered the from diabetes mellitus within a year.

Discussion

Schizophrenia remains an inadequately treated disease irrespective of the socioeconomic environment in a specific country and the cultural status of the affected individuals. Hospitalization had been for many decades the basis of schizophrenia management partly due to the failure of available antipsychotic medications to provide an effective and without side effects therapeutic outcome. The personal cost of schizophrenia is often catastrophic. Sufferers, even before symptoms are overt, frequently find it impossible to achieve expected levels of functioning, and quickly encounter problems with employment and social stability. Even worst, suicide remains the major cause of death for patients with schizophrenia, 40% of them attempting at least once and 10% succeeding a suicide. Newer antipsychotic medications with a more favorable safety profile are available the since the last decade, something that made doctors therapeutic interventions less dependable to in-hospital interventions both from an efficacy and also from side effects management point of view. At the same time public health policies have realized the need for a less dependent to in-hospital treatments of mental disorders and a more society centered therapeutic interventions.

There are no diagnostic physical tests for schizophrenia, it is defined by symptoms and signs. Treatments for schizophrenia are divided into the so-called "physical interventions" of drugs, the psychological and social managements and, rarely, the electroconvulsive therapy (ECT). The first antipsychotic drug used to treat schizophrenia was chlorpromazine. Since the discovery of the effects of chlorpromazine, treatment of schizophrenia has relied on antipsychotic drugs that target dopamine D2 receptors. Despite treatment with available neuroleptic agents, it is estimated that 10–20% of schizophrenic patients remain symptomatic and a good fraction of these patients severely symptomatic. In addition to those patients who are refractory to treatment, many others cannot tolerate typical neuroleptics because of their adverse effects, particularly extrapyramidal side effects, which also affect the patients' response to treatment due to lower compliance. Clozapine, the first atypical neuroleptic, appears to have some

advantages over conventional neuroleptics.[4,5] The drug is less tightly bound to the D2-receptor and D2-receptor antagonism is no longer the sole therapeutic mechanism, as clozapine affects also D1, D4 dopamine receptors and norepinephrine and serotonin, 5-HT_2 receptors.[6] It carries a negligible risk of acute extrapyramidal syndrome and tardive dyskinesia but definitely less from the risk that accompanies the use of typical neuroleptics. Clozapine appears to have potential benefits for secondary negative symptoms and certain domain of cognitive dysfunction. Several studies have shown clozapine's efficacy in treatment resistant schizophrenia.[1,7–9] In addition to its superior clinical efficacy, clozapine appears to suppress abnormal involuntary movements, and has been shown to have a lower propensity to cause extrapyramidal symptoms and tardive dyskinesia.[10,11] Other side effects include sedation, weight gain, diabetes mellitus, may be in association with weight gain and seizures. A rare but potentially side effect is myocarditis.[12] Clozapine use is associated with a hematological abnormality in approximately 1–1.5% of patients treated with this drug. A reduction in the WBC count and more specifically of the neutrophilic line leaves the patient susceptible to opportunistic infections with a bad prognosis if this is not reversed and properly treated. For this reason weekly full blood counts for the first 18 weeks, and monthly thereafter, including the first four weeks after the patient has discontinued the drug[13] are always needed in all patients treated with clozapine.

In this study the patients suffer from acute, newly diagnosed schizophrenia. It was the first time that these patients presented schizophrenic symptoms in their life. They received common antipsychotic drugs for 3–4 months as first-line therapy, in which they have not responded. They were characterized as treatment-resistant schizophrenics and then received clozapine. In this acute, first episode of schizophrenia is difficult to record the negative symptoms that these patients present, as positive symptoms are those which prevail in an acute, first episode of schizophrenia. In order to establish the efficacy of clozapine GAF and PANSS scale have been recorded prior to initiation of clozapine and at the end of observational period. Clozapine is introduced in a dose-incremental manner, with an average effective dose of about 300–600 mg/day. Both scales showed that treatment with clozapine improves patients' function, since there was a significant improvement in both GAF and PANSS scales. After treatment with clozapine, negative symptoms for the PANSS scale were recorded. The results showed that were 6±5.4 mean points of negative symptoms, in PANSS scale, at the end of observational period. We had tried also to see the effect of clozapine on the social status of our patients despite the number of these patients was not allowing us to make a proper statistical analysis. It was observed a marked change in both marital and employment status, since 5 patients got married, although one afterwards got a divorce, and in employment status, since 4 patients got employed and 6 students became college or university students.

For assessing the safety of clozapine WBC were monitored every week for the first 18 weeks and then monthly, for the risk of agranulocytosis, as well as the glucose levels, for the risk of developing diabetes mellitus. The results showed that in this study the use of clozapine was safe, as only one out of the 66 patients developed agranulocytosis after 10 months with clozapine treatment, and only one out of the 66 patients presented with higher glucose blood levels suggested of diabetes mellitus. Both patients recovered after the discontinuation of clozapine.

The use of clozapine at an outpatient setting within the Cyprus social and medical environment seems to be an effective, safe and well acceptable by patients and their families practice. We have been able to keep our patients mostly symptoms free and we have good reasons to believe that their quality of life has improved significantly. Potential risks of clozapine use at an outpatient setting can be safely managed. For these reasons we believe that schizophrenic patients not reaching their premorbid state after the use of two antipsychotics within a reasonable period of time they should be given a clozapine trial.

Η αξιολόγηση της θεραπείας κλοζαπίνης σε μη νοσηλευόμενους ανθεκτικούς σε θεραπεία σχιζοφρενικούς ασθενείς

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Η κλοζαπίνη είναι ένα άτυπο αντιψυχωσικό φάρμακο με ένδειξη για ασθενείς που πάσχουν από σχιζοφρένεια και δεν ανταποκρίνονται στη συνήθη αντιψυχωσική θεραπεία. Ο στόχος αυτής της μελέτης ήταν να αξιολογήσει την ανταπόκριση στη θεραπεία με κλοζαπίνη και να διερευνήσει τη συνολική λειτουργία μια ομάδας μη-νοσηλευόμενων ασθενών με σχιζοφρένεια, ανθεκτικούς στην καθιερωμένη θεραπεία. Δεδομένα από 66 σχιζοφρενείς ασθενείς, 28 γυναίκες και 38 άνδρες, με αντοχή στη θεραπεία εξετάστηκαν αναδρομικά με το Global Assessment of Functioning Scale (GAF) και το Positive and Negative Syndrome Scale (PANSS), ενώ έγινε και αξιολόγηση των λευκών αιμοσφαιρίων (WBC). Βάσει της κλίμακας GAF, εκτιμήθηκε σημαντική βελτίωση στη λειτουργία αυτών των ασθενών (49,7±23,6 SD, P<0,001) στο τέλος της περιόδου θεραπείας με κλοζαπίνη. Επιπλέον, χρησιμοποιώντας το PANSS, φάνηκε ότι η θεραπεία με κλοζαπίνη βελτίωσε σημαντικά τα αρνητικά και θετικά συμπτώματα καθώς και τη γενική ψυχοπαθολογία αυτής της ομάδας ασθενών. Η μείωση των WBC ήταν μέσα στα αναμενόμενα επίπεδα. Δεν διαπιστώθηκε καμία αρνητική επίδραση της θεραπείας στα WBC στους 65 από τους 66 ασθενείς. Συμπερασματικά, η χορήγηση κλοζαπίνης σε μια ομάδα ασθενών που πάσχουν από σχιζοφρένεια, ανθεκτικών στη συνήθη αντιψυχωσική θεραπεία, βελτιώνει τη συνολική λειτουργία των ασθενών, χωρίς να παραβλάπτει το προφίλ ασφαλείας των ασθενών.

Λέξεις ευρετηρίου: Σχιζοφρένεια, αντιψυχωσική θεραπεία, μη-νοσηλευόμενοι ασθενείς, κλοζαπίνη, λειτουργία, κλίμακα GAF, κλίμακα PANSS.

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