

Incidence of agranulocytosis adverse effect of antipsychotic drugs in patients with schizophrenia

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Received: 12-05-2022, **Revised:** 10-06-2022, **Accepted:** 14-06-2022, **Published:** 30-06-2022

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HOW TO CITE THIS

Aburawi et al. (2022) Incidence of agranulocytosis adverse effect of antipsychotic drugs in patients with schizophrenia. *Mediterr J Pharm Pharm Sci.* 2 (2): 52-63. [Article number: 68]. <https://doi.org/10.5281/zenodo.6780500>

Keywords: Antipsychotics, kidney function, Libya, lipid profile, liver function, schizophrenia

Abstract: Schizophrenia is treated with antipsychotic drugs and is a chronic neuropsychiatric disorder. The influence of antipsychotics on the cytokine systems may be responsible for their clinical efficacy in schizophrenia. Granulocytopenia and agranulocytosis are severe side effects of antipsychotic therapy. The objective of this study was to estimate the incidence of drug-associated agranulocytosis in newly diagnosed schizophrenic patients and to evaluate the risk factors and outcomes. Seven participant groups were designed. Healthy persons as control. Schizophrenic patients before treatment. Schizophrenic patients after one month of treatment. Schizophrenic patients after two months of treatment. Schizophrenic patients after three months of treatment. Schizophrenic patients after chronic treatments. Schizophrenic patients one month after chronic treatment. This study included screening for the expression and function of circulating leukocyte granulocyte-macrophage colony-stimulating factor receptors, and screening of the patient's biochemistry and haematology picture. Granulocyte-macrophage colony-stimulating factor expression was decreased after antipsychotic treatment for one month and continued to decline after two months of treatment. Granulocyte-macrophage colony-stimulating factor expression starts to increase after the two months treatment and continues growing in controls or newly diagnosed schizophrenics or after chronic treatment. Complete blood counts were not changed compared. Liver function showed a transient increase in serum alkaline phosphatase after one and two months of treatment. All other parameters were not changed. Kidney function showed that urea and creatinine levels were within the normal range during the different treatments. Concerning lipid profile, low density lipoprotein levels were increased after one month, two months of treatment and after chronic administration of the antipsychotic drugs. It is concluded that antipsychotic treatment produces a decrease in granulocyte-macrophage colony-stimulating factor expression; the decrease reaches the maximum effect after two months, and then starts to increase back to normal levels. A transient increase in serum alkaline phosphatase in the first two months of treatment. Urea and creatinine levels and lipid profile were within normal range, except low density lipoproteins levels were increased during the two months of treatment and after chronic administration of the antipsychotic drugs.

Introduction

Schizophrenia is a common psychiatric disorder of high incidence, affecting approximately 1.0% of the world population [1]. It has been reported that genetic, environmental, neurobiology, psychological and social processes are important contributory factors [2]. Antipsychotic drugs, in particular chlorpromazine and atypical compound clozapine, influence the production of cytokines which are pivotal humoral mediators of infection and inflammation. They play a significant role in hematopoiesis and autoimmunity. Cytokines have numerous effects on the central nervous system (CNS), they may mediate the effects of antipsychotic drugs on brain functions [3]. Agranulocytosis is a syndrome characterized by severe neutropenia and manifested by sudden onset of signs and symptoms of bacterial infection [4]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is one of a family of glycoprotein cytokines that have potent effects in stimulating the proliferation, maturation and function of hematopoietic cells. GM-CSF acts as a potent growth factor *in-vitro* and *in-vivo*, stimulating proliferation and maturation of myeloid progenitor cells, giving rise to neutrophilic and eosinophilic granulocytes and monocytes [5, 6]. There is accumulating evidence of its critical role in CNS repair via the expression of brain-derived neurotrophic factor, a trophic factor that has been associated with psychiatric illness. This is consistent with broader evidence of the role of GM-CSF and IL-3 in the CNS, including neuroprotection, communication across the blood-brain barrier and neurotransmitter modulation (particularly of acetylcholine and GABA) [6]. The objectives of this study were to estimate the incidence of drug-associated agranulocytosis in newly diagnosed schizophrenic patients in Libya and to evaluate risk factors and outcomes.

Materials and methods

Materials: BD pharmingen™ (R-phycoerythrin-conjugated mouse anti-human CD116"GM-CSF Receptor & CHAIN" Monoclonal antibody). BD logo and all other trademarks are property of Becton, Dickinson and Company. Ethyl alcohol (75.0% as an antiseptic, disinfectant, from Purell product, UK (purchased from Milton Keynes)). Sheath fluid from Becton, Dickinson Company, GmbH, Tullastrasse, Heidelberg, Germany.

Chemicals for FACS Calibur flow cytometer: The human granulocyte macrophage colony-stimulating factor receptor complex (hGMCSFR-M1) antibody was purchased from Becton Dickinson, Tullastrasse, Heidelberg, Germany. Cell back was used as the diluent, which was obtained from Sysmex Europe, Bornbach Norderstedt, Germany. Stromatolyser®-WH was purchased from Sysmex Europe, Bornbach, Norderstedt, Germany.

Chemicals for kidney function: Urea reagents, creatinine reagents, uric reagents and electrolytes reagents (sodium and potassium) were purchased from Roche Diagnostics Mannheim, Germany. Chemicals for lipid profile: cholesterol reagent, triglycerides reagent, low-density lipoprotein reagents, high-density lipoprotein reagents were from Roche Diagnostics Mannheim, Germany. Chemicals for liver function: Alkaline phosphatase reagents, gamma-glutamyl transferase reagent, glutamate pyruvate transaminase, bilirubin reagents (working solutions) and glutamate oxaloacetate transaminase reagents were purchased from Roche Diagnostics Mannheim, Germany. Chemicals for hematology picture: Cell back, Stromatolyser® -WH and cell clean were purchased from Sysmex Corporation, Wakinohama-Kaigandori, Chuo Ku, Kobe, Japan.

Instruments: Sysmex.kx-21n analyzer: Sysmex corporation1-5-1 Wakinohama-Kaigandori, Chuo ku, Kobe 651-0073, Japan. ROCHE DIAGNOSTICS-COBAS INTEGRA® 400 PLUS: Roche. Diagnostic GMmbH, Sandhofer Strabe Mannheim, Germany. Abbott Diagnostics-ARCHITECT c8000: Abbott GmbH Diagnostika Max-Planck-Ring 2, 65205 Wiesbaden, Germany. Heraeus centrifuge (ROCHE Company): Ludwig-Wagner-Str, Wiesloch, Germany. Becton-Dickinson FACS Calibur flow cytometer: purchased from Becton Dickinson GmbH, Tullastrasse Heidelberg, Germany.

Tools: BD microlance™ 3: (0.6 × 25mm) from Becton Dickinson S.A FRAGA (HUESCAL), Spain. BD Discardit™II: (syringe 5 ml) from Becton Dickinson S.A FRAGA (HUESCAL), Spain. BD Vacutainer®: (K2E 5.4 mg, plus blood collection tubes) Red blood 3.0 ml made in Loughborough, UK. BD Vacutainer®: (SST™II Advance, plus blood collection tubes), white blood Loughborough, UK. ICE CHEST: container from Sitra Company, Tunisia. Cup sample: specified for Cobas Integra 400 and Architect C8000 from Abbottm USA.

Design of the study: The participants were recruited from AL-RAZI hospital in Tripoli, Libya and different regions in Tripoli during the period of 2010 and 2011. Ethical approval from the scientific committee of the hospital and the University of Tripoli was obtained before starting the study. Seven participant groups are involved in this study. Group 1: Healthy persons without any disease (n=51, 26M & 25F). Group 2: Schizophrenic patients before treatment (n=12, 5M & 7F). Group 3: Schizophrenic patients after one month of treatment (n=12, 5M & 7F). Group 4: Schizophrenic patients after two months of treatment (n=12, 5M & 7F). Group 5: Schizophrenic patients after three months of treatment (n=12, 5M & 7F). Group 6: Schizophrenic patients after chronic treatments (n=63, 34M & 29F). Group 7: Schizophrenic patients one month after chronic treatment (n=63, 34M & 29F). Patients involved in group 2, are the same patients involved in groups 3, 4 and 5 as a follow-up. While the patients involved in group 6 are the same patients involved in group 7. The age of healthy volunteers ranges from 33-53 years old while the age of patients ranges between 31-56 years old.

Kidney function: measuring the levels of urea, creatinine, uric acid and electrolytes (sodium and potassium) in serum. **Liver function:** measuring the serum levels of cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, alkaline phosphatase, gamma-glutamyltransferase, glutamate pyruvate transaminase, bilirubin and glutamate oxaloacetate transaminase.

Haematology: for parameters of complete blood picture.

GM-CSF expression Procedure: Blood samples (3.0 ml) are taken from the donors in EDTA tubes. By using a micropipette, transfer 0.04 ml of CD116 to a test tube containing 0.50 ml of collected blood. Mix the mixture by vortex, and keep the tube at room temperature in the dark for fifteen minutes. Add 500 µl from the analyzes buffer (for RBC lysis) and 2 ml of distilled water to the mixture of step 2, mix and keep the tube in the dark for another fifteen minutes. Add one ml of cell wash then mix and centrifuge at speed (1500 cycle/sec) for 10 minutes. Remove the supernatant and one ml of cell wash to the residue and centrifuge for five minutes. Finally, discard the supernatant and add eight drops of cell fixator or staining to the mixture. Samples are analyzed by a flow cytometer system.

Biochemistry: Samples are processed in the following steps: Blood sample (5 ml) is collected from the vein in Silica (Clot Activator)/Gel tube; these tubes should be labeled appropriately before the specimen collection. Items include the patient's complete name and age identification number. Centrifuge for one minute to separate the serum. Transfer 100 µl of serum to the sample cup (specific for Cobas Integra 400, architect C 8000). Put the sample cup tubes on the rack that are inserted into the rack position area in the system (Cobas Integra 400, architect C8000). All required reagents, diluents, cleaners, calibrators and controls must be fulfilled before successfully running any test on the systems (Cobas Integra 400, architect C8000). Use the options tab of the systems to specify the parameters needed for biochemical analysis of the specimens. The biochemical tests are uric acid and electrolytes (sodium and potassium), kidney function test (urea and creatinine), liver function test (alkaline phosphatase, glutamyl transferase, glutamate pyruvate transferase, bilirubin direct, glutamate oxaloacetate transferase) and lipid profile (cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein).

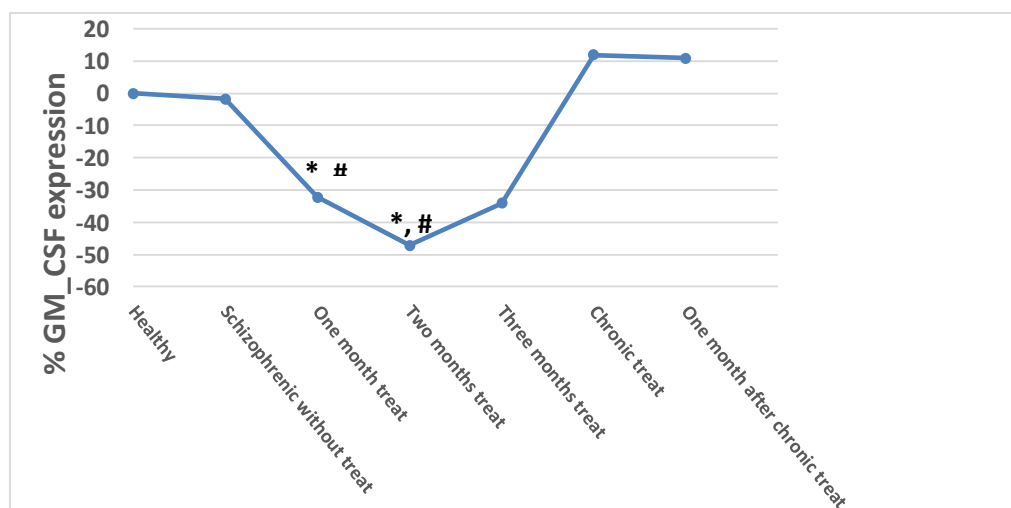
Hematology: Completely automatic procedure in each analysis mode: samples are processed in the following steps: A specified amount of blood (3 ml) is collected in EDTA containing tube from the vein. Mixing the sample sufficiently. Set the tube to the sample probe, and press the start switch of the system. Whole blood (50 μ l) has aspirated automatically from the sample probe into the sample rotor valve.

Statistical analysis: Descriptive statistical analysis was carried out using the computer program SPSS (version 26). To verify whether the data were parametric, the Kolmogrove-Simirnov test, and maximum deviation test for goodness of fit were applied. If the parameters were parametric, treatments were compared by one-way ANOVA, post-hoc test as an LSD test. If the parameters were non-parametric, then, individual treatments were compared by using a Mann-Whitney *U*-test. The differences were considered significant at *p* value<0.05. The values are expressed as mean \pm standard error.

Results

Granulocyte-macrophage colony-stimulating factor (GM-CSF) expression and levels: GM-CSF expression was not significantly changed in newly diagnosed schizophrenics before starting treatment (*p*=0.88) but it was significantly decreased after one month (*p*=0.02) and in two months (*p*=0.01) of treatment compared to healthy volunteers. While GM-CSF expression after three months of treatment, chronic treatments or even one month after chronic treatment did not show any significant change compared to healthy volunteers (**Figure 1**). GM-CSF expression after treatment for one or two months was decreased significantly compared to schizophrenics before starting treatment (*p*=0.07 and *p*=0.02, respectively). GM-CSF expression of schizophrenic patients after three months of treatment and after chronic or one month after chronic treatment did not show any change compared to schizophrenics before starting treatment (**Figure 1**).

Figure 1: Percentage changes of GM-CSF expression in healthy and schizophrenic patients



*Significantly different from healthy; #Significantly different from patient without treatment

Hematology picture

White blood cells (WBCs): WBCs was increased significantly after treatment for one month (8.2125 ± 1.187 , *p*=0.04) or even after chronic treatment (7.6032 ± 0.338 , *p*=0.01) compared to healthy volunteers (6.5000 ± 0.250). Although the levels were within the normal range. While WBC after two months (6.7714 ± 0.448), three months (6.3333 ± 0.664) of treatment and chronic treatment even after one month later (6.8400 ± 0.410) did not show any significant change compared to healthy volunteers. However, WBCs was not changed in patients with treatment for one, two and three months after being diagnosed as schizophrenics, or even chronic and chronic one month later compared to those without treatment (7.7167 ± 0.619).

Red blood cells (RBCs): RBCs count was decreased significantly in schizophrenics with chronic treatment (4.5843 ± 0.062 , $p=0.03$) compared to healthy volunteers (4.7869 ± 0.062), although they were within the normal range. While RBCs of schizophrenics without treatment (4.6192 ± 0.171) and after one (4.7350 ± 0.261), two months (4.4614 ± 0.235), three months (4.8400 ± 0.354) of treatment, or even chronic and one month (4.6060 ± 0.091) later did not show any significant change compared to healthy volunteers. RBCs was not changed in patients with treatment for one, two and three months after being diagnosed as schizophrenics, or even chronic and chronic one month later compared to the patients without treatments.

Hemoglobin (Hgb): Hgb levels were not changed in all the groups of schizophrenics (before and after treatment) compared to healthy volunteers and to Hgb levels of schizophrenic patients before starting treatment. Normal range for males: 11.3-15.7 g/dl, (n=124) and for females: 9.9-13.6 g/dl, (n=117).

Hematocrit (HCT): HCT levels were not changed in all the groups of schizophrenics (before and after treatment) compared to healthy volunteers as well as to HCT levels of schizophrenics before starting treatment. HCT units for males: 32.6-47.5% (n=124), for females: 30.2-42.3%, (n=117).

Platelets (PLTs): The PLT count was increased significantly in newly diagnosed schizophrenic patients before starting treatments (319.2500 ± 35.028 , $p=0.01$) compared to healthy volunteers (250.5588 ± 10.284). While PLT after one (261.7500 ± 21.368), two (232.0000 ± 11.680) and three months (225.3333 ± 40.596) of treatment or even of chronic treatment in years (264.0159 ± 11.745) and chronic one month (281.2000 ± 15.256) later did not show any significant change compared to healthy volunteers. All PLT counts were within the normal levels. PLT count, after treatment for two months or after chronic treatment was decreased significantly compared to PLT count of schizophrenics without treatment ($p=0.03$ and $p=0.03$, respectively). PLT was not changed in patients after one month or three months of treatment as schizophrenics and chronic one month later compared to patients without treatments. All PLT counts in different groups are within the normal range.

Mean corpuscular volume (MCV): MCV was increased significantly in schizophrenics after treatment for two months (90.7857 ± 1.606 , $p=0.01$) also after chronic treatment in years (87.4111 ± 0.842 , $p=0.02$) and chronic one month later (89.3480 ± 1.351 , $p=0.01$) compared to healthy volunteers (84.7882 ± 0.866). While MCV in schizophrenics without treatment (88.0833 ± 1.699) or after one month (89.3750 ± 1.468) and three months (88.1667 ± 2.345) of treatment did not show any change. MCV was not changed in patients with treatment for one, two and three months after being diagnosed as schizophrenics, or even after chronic treatment or chronic one month later compared to the patients without treatments.

Mean corpuscular haemoglobin (MCH): The MCH levels did not show any change in different treated groups compared to healthy volunteers; also, MCH in all the treated groups was not changed compared to schizophrenic patients before starting treatment.

Kidney function

Serum urea: The levels of urea were decreased significantly in chronic schizophrenics (15.5 ± 1.16 , $p=0.01$) compared to healthy volunteers (19.0 ± 1.46). While urea of newly diagnosed (14.4 ± 2.05), after one (21.0 ± 3.69), two (14.7 ± 3.37) and three months (19.0 ± 9.00) of treatment, as well as one month after chronic patients (15.9 ± 1.86) did not show any change compared to healthy volunteers; all the urea levels in different groups were within the normal levels. Urea of the schizophrenics before starting treatment, after one, two, three months of treatment and after chronic treatments, or treatment one month after chronic treatment was not changed.

Serum creatinine: The creatinine levels were not changed in different treated groups compared to healthy volunteers; all creatinine levels were within the normal range.

Serum Uric acid: Uric acid levels did not show any change in different treated groups compared to healthy volunteers or schizophrenics before starting treatments. All uric acid levels were within the normal levels in different treated groups.

Serum sodium: Levels of sodium were decreased significantly in chronically treated schizophrenics (142.8 ± 1.00 , $p=0.05$) compared to sodium-healthy volunteers (144.4 ± 0.98). While sodium in newly diagnosed schizophrenics (141.5 ± 1.49), patients after one (140.5 ± 1.82), two (141.6 ± 2.38), three months (140.6 ± 4.33) of treatment or even after one month of chronic treatment (142.4 ± 1.14) did not show any changes compared healthy volunteers. Sodium levels were not changed in patients with treatment for one, two and three months after being diagnosed as schizophrenics and of chronic treatments or even after one month of chronic treatment compared to the patients without treatments.

Serum potassium: Potassium levels did not show any change in newly diagnosed, schizophrenics before starting treatments and after treatment for one, two, three months, also after chronic treatment or even after one month compared to healthy volunteers. Potassium levels of schizophrenics treated for one, two, and three, even after chronic treatments and one month after chronic administration were not changed compared to levels in newly diagnosed patients without treatment.

Lipid profile

Serum cholesterol: Although cholesterol levels were increased significantly in schizophrenics after treatment for one month (189.0 ± 10.95 , $p=0.04$) and chronic treatment after one month later (180.0 ± 7.42 , $p=0.036$) compared to healthy volunteers (160.4 ± 4.27), the levels are within the normal range. While cholesterol of the newly diagnosed with schizophrenia (159.7 ± 8.47) before starting treatment and after treatment for two (179.3 ± 11.7) and three months (196.3 ± 13.09) or even chronic treatments (170.0 ± 5.42) did not show any change. Cholesterol levels did not show any difference in all different treatments in comparison with control. All cholesterol levels are within the normal range.

Serum triglyceride (TG): TG levels were increased significantly in schizophrenics after treatment for one (159.28 ± 24.6 , $p=0.02$), two (161.62 ± 31.75 , $p=0.01$) and three months (198.33 ± 29.61 , $p=0.01$) or even chronic treatments (140.07 ± 9.01 , $p=0.01$) and chronic after one month later (141.91 ± 14.45 , $p=0.01$) compared to healthy volunteers (99.26 ± 8.26). While TG of schizophrenics without treatments (92.00 ± 16.93) did not show any change compared to healthy volunteers. There was a significant increase in TG after treatment for one ($p=0.03$), two ($p=0.02$) and three months ($p=0.01$) when compared to schizophrenics without treatment. TG of chronic treatment schizophrenics ($p=0.02$) and chronic one month later ($p=0.03$) were increased significantly compared to schizophrenics without treatment.

Serum low-density lipoprotein (LDL): LDL levels in schizophrenic patients after treatment for one (154.66 ± 21.97 , $p=0.01$), two months (147.50 ± 6.5 , $p=0.03$) and chronic one month later (122.05 ± 6.82 , $p=0.01$) were high increased significantly compared to LDL of healthy volunteers (96.63 ± 5.07). While the LDL of the newly diagnosed schizophrenics before starting treatment (111.14 ± 18.84) and chronic treatments (106.96 ± 5.2) did not show any change compared to controls. LDL levels were not changed in patients after treatment for one and two months or even after chronic treatment and one month later compared to controls.

Serum high density lipoprotein (HDL): HDL levels were decreased significantly in schizophrenics after chronic treatment (48.94 ± 1.96 , $p=0.01$) compared to controls (57.48 ± 2.25). While HDL levels after one (59.14 ± 5.81), two (49.75 ± 3.33) and three (46.50 ± 12.5) months of treatment or after being diagnosed as schizophrenia without treatment (56.63 ± 3.89) or even after chronic one month later (56.52 ± 2.69) did not show significant change. Levels of HDL were not changed in patients after treatment for one, two and three months, also chronic treatment and chronic one month later compared to patients without treatments.

Liver function

Serum alkaline phosphatase (ALP): The levels of ALP were significantly increased in newly diagnosed schizophrenic before starting treatments (102.27 ± 23.13) or even after one month (113.14 ± 19.76 , $p=0.01$) and after two months (139.50 ± 55.49) compared to ALP in controls (71.95 ± 2.77); although the levels were within the normal range. While ALP levels after three months of treatment (87.50 ± 2.50), chronic treatment (87.47 ± 3.54) or even after chronic one month later (89.60 ± 4.84) did not show any change compared to controls. The levels of ALP did not show any significant change after treatment for one, two and three months or even after chronic (years) and after chronic one month later compared to schizophrenics without treatment.

Serum gamma-glutamyl transferase (GGT): The levels of GGT were significantly increased in the schizophrenics after treatment for one month (49.00 ± 19.34 , $p=0.01$) and two months (51.57 ± 18.82 , $p=0.03$) compared to healthy volunteers (22.02 ± 2.85) and to schizophrenics without treatment ($p=0.053$ and $p=0.01$, respectively). While GGT levels in newly diagnosed as schizophrenics (23.18 ± 5.81) did not show any change compared to healthy volunteers, in patients with chronic treatment (31.00 ± 3.71) and after one month later of treatment (29.54 ± 6.15). All the levels were within the normal range. Only one patient treated for three months offered a sample for analysis, the rest of the samples were lost.

Serum glutamate pyruvate transaminase (GPT): GPT levels were increased significantly in schizophrenics after treatment for one month (27.87 ± 5.83 , $p=0.03$) and two months (28.33 ± 4.58 , $p=0.01$) compared to controls (19.35 ± 2.92). While serum GPT levels of schizophrenics without treatment (15.50 ± 2.31), after three months of treatment (20.33 ± 4.48) and chronic treatments (20.44 ± 1.68) and even one month after chronic treatment (23.00 ± 3.16) did not show any changes compared to control. All the different treatments did not show any significant difference in GPT compared to schizophrenics without treatment; all the levels were within the normal range.

Serum bilirubin: Bilirubin levels were decreased significantly in schizophrenics after chronic treatment (0.300 ± 0.0223 , $p=0.01$) and chronic one month later (0.350 ± 0.02850 , $p=0.01$) compared to healthy volunteers (0.666 ± 0.08730). While bilirubin in newly diagnosed schizophrenics before starting treatment (0.722 ± 0.20600), after one month (0.625 ± 0.2136), two months (0.571 ± 0.21900) and after three months of treatment (1.250 ± 0.950) did not show any change. Patients after chronic treatments ($p=0.01$) and chronic one month later ($p=0.03$) showed a significant decrease in bilirubin compared to schizophrenics without treatment. The levels were not changed in patients with treatment for one, two and three months after being diagnosed as schizophrenics, compared to the patients without treatments.

Serum glutamate oxaloacetate transaminase GOT: GOT did not show any change in newly diagnosed, schizophrenics before starting treatments, after treatment for one, two and three months or even after chronic and chronic one month later compared to healthy volunteers; all GOT levels were within the normal range. All different treatments showed no significant differences in GOT levels compared to schizophrenics before starting treatment, all the levels are within the normal range.

Discussion

Schizophrenia is a severe neuropsychiatric disorder that represents the 18th leading cause of years lived with disability globally [7] and has an estimated point prevalence of 0.5% to 1.0% [8]. Functional and structural dysconnectivity are among the most reproducible neurophysiological abnormalities associated with schizophrenia [9-13]. The influence of antipsychotics on the cytokine system may be responsible for the clinical efficacy in schizophrenia [14]. Clozapine and haloperidol, at concentrations within the therapeutic range, may exert immunosuppressive effects [15]. Granulocytopenia (decrease in a number of granulocytes) and agranulocytosis (a condition of bone marrow that does not make enough neutrophils) are severe side

effects of antipsychotic therapy. Antipsychotics may produce bone marrow suppression, formation of antibodies against hematopoietic precursors or involve peripheral destruction of cells [16]. Most drug-induced agranulocytosis is dose-dependent [16, 17]. Oxidation of clozapine by neutrophil generated hypochlorous acid via NADPH oxidase/myeloperoxidase system has been demonstrated [18-20]. These ions are normally detoxified by reduced glutathione. However, the ions may also bind to neutrophils to cause cell death or could cause oxidative stress-induced neutrophil apoptosis [21]. Antineutrophil antibodies, are possibly generated by the reaction of nitrenium ions with neutrophil proteins resulting in hapten formation that may be involved in etiology of clozapine-induced neutropenia [22]. Oxidative metabolism of olanzapine gives rise to a nitrenium ion and this may produce leucopenia and neutropenia [23-26]. After antipsychotic drug discontinuation, treatment with GM-CSF, a glycoprotein, was shown to stimulate the proliferation of precursor cells in bone marrow and their differentiation into granulocytes and macrophages was initiated. Treatment with GM-CSF may lower the risks associated with antipsychotic drug-induced agranulocytosis. This indicates that the levels or the expression of GM-CSF are lower than normal [27]. Oren et al. [28] reported that clozapine-induced agranulocytosis is usually reversible after discontinuation of the drug. A patient who developed agranulocytosis after the termination of clozapine responded to treatment with GM-CSF. In this study, GM-CSF was decreased in the first eight weeks of the antipsychotic treatment. It is probable that antipsychotic reduces GM-CSF in the first eight weeks. The increase may be due to tolerance toward antipsychotic effect or until hematologic recovery. GM-CSF is a monomeric glycoprotein secreted by macrophages, T cells, mast cells, NK cells, endothelial cells and fibroblasts that functions as a cytokine. GM-CSF is a white blood cell growth factor; GM-CSF stimulates stem cells to produce granulocytes (neutrophils, eosinophils and basophils) and monocytes [29]. GM-CSF, a glycoprotein with hormonal properties, is produced by several cell types, most of which exist outside the CNS. GM-CSF, however, affects the CNS. If capable of crossing from blood to CNS, GM-CSF might be an important signaling molecule between the CNS and periphery. GM-CSF crosses the blood-brain barrier and blood-spinal cord barrier; it is demonstrated that a saturable mechanism transports of GM-CSF intact from blood to CNS [30]. Granulocytopenia and agranulocytosis are severe side effects of antipsychotic therapy. Patients suffering from agranulocytosis are extremely endangered by infectious diseases for 3-4 weeks until hematologic recovery. A patient in whom severe agranulocytosis developed after seven weeks of antipsychotic is presented. After antipsychotic discontinuation, and treatment with GM-CSF, the total granulocyte count rose from 63 per cu mm to a value greater than 1500 per cu mm within five days without complications or major side effects [27]. GM-CSF started to increase after eight weeks until hematologic recovery [27]. It is suggested that clozapine-mediated inhibition of the release of GM-CSF is involved in clozapine-induced agranulocytosis [31]. Neutrophil count, in the present study, was within the normal levels which indicates that a decrease in the release of GM-CSF may affect the function and not the count number of neutrophils. Thus, GM-CSF was decreased in the first eight weeks after the beginning of treatment with antipsychotic drugs; GM-CSF, which is considered neurotropic cytokine, is consumed in the first few weeks in repairing CNS disorder in the immune system. The decrease in GM-CSF was significant in the first eight weeks which is associated with the disappearance of positive results. It is concluded that antipsychotic decreases GM-CSF protein, therefore it may produce agranulocytosis. Although the WBC in all different treatments is within the normal count, antipsychotics may reduce the function and not WBC count. GM-CSF is a hematopoietic cytokine that has the potential for clinical application. The biological effects of GM-CSF have well been characterized and included stimulation of bone marrow hematopoietic stem cell proliferation and inhibition of apoptosis of hematopoietic cells [32]. If GM-CSF is given prior to MPTP (n 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine) protected nigral dopaminergic neurons; GM-CSF modulation of immunity could be of clinical benefit for Parkinson's disease (PD) [33]. GM-CSF is involved in the recovery and control of cell death following spinal cord injury [34]. It is demonstrated that GM-CSF protects dopaminergic neurons from MPTP-induced death [33]. Notably, GM-CSF is neuroprotective in Parkinson's

models, by decreasing the proteins associated with neuronal apoptosis, Bcl-2, and Bax and inducing brain-derived neurotrophic factor (BDNF) [32, 35, 36]. Administration of GM-CSF *in vivo* protected dopaminergic neurons in the substantia nigra and improved locomotor behavior in the mice MPTP model of PD [32].

Antipsychotic drugs decrease GM-CSF during the first eight weeks, where the lowest levels were in the 8th week. Since GM-CSF is responsible for protecting the dopamine neurons, consequently, the decrease in GM-CSF will lead to a decrease in dopamine levels. This might be an explanation for the mechanism of action of antipsychotics in decreasing dopamine levels where the clinical response of antipsychotics may be through a decrease in GM-CSF. Because the positive symptoms generally respond well to medication [37], they disappear gradually through the first eight weeks. There is a correlation between NMDA-receptor and GM-CSF in different brain areas. NMDA receptor hypofunction contributes to the symptoms of schizophrenia [38]. In patients with schizophrenia, post-mortem studies showed changes in the composition of NMDAR subunits in different human brain areas [39]. Antipsychotic medication can decrease NMDARs through the change in the composition of their subunits in the thalamus and hippocampus [40]. In the hippocampus, antipsychotic drugs decrease the activity of NMDAR receptors, leading to a decrease in glutamatergic activity [41]. Olanzapine, clozapine and haloperidol decreased NMDAR expression in the rat thalamus [42]. Clozapine may also act as Mg^{2+} and voltage-independent NMDAR channel blocker [43]. Haloperidol exerts an antagonistic activity against NMDARs, binding with a specific allosteric site of NR2B [44]. Antipsychotic medication may maintain and escalate hypofrontality in schizophrenia, by inhibiting NMDA receptor activity in the corticolimbothalamic circuit in the human brain [40]. Hypo-frontality is a state of decreased cerebral blood flow in the prefrontal cortex of the brain; it is a symptomatic condition of schizophrenia [45]. GM-CSF levels were down-regulated after repeated ketamine administration [46]. Ketamine is noncompetitive NMDA glutamate receptor antagonist [47]. Therefore, the decrease in GM-CSF observed in this study may be due to the inhibition of NMDA receptor activity by the antipsychotic drugs. Liver function abnormalities were found in about 10% of the schizophrenic patients treated with antipsychotics [48]. Antipsychotics elevate ALP which is usually arising within the first eight weeks of treatment [49, 50]. Pharmacological and clinical factors could be related to these alterations [48]. ALPs are present in many human tissues, including bone, intestine, kidney, liver, placenta and white blood cells [51]. Damage to these tissues causes the release of ALP into the bloodstream [52]. In this study with regard to liver function, there was an increase in ALP after two-month treatment, which is due to antipsychotic therapy. While kidney function, the investigation revealed within the normal range. Patients treated with antipsychotics are at a higher risk for the development of lipid abnormalities than the general population [53]. Antipsychotic-induced metabolic adverse effects in the clinical setting [54]. The molecular mechanisms mediating metabolic disturbances are incompletely understood [54]. In 1965, haloperidol was demonstrated to inhibit cholesterol biosynthesis [55]. It is demonstrated that haloperidol, clozapine, risperidone and ziprasidone reduce *de novo* cholesterol biosynthesis. This occurs through the inhibition of several enzymatic steps in the later part of the cholesterol biosynthesis pathway, leading to the accumulation of various cholesterol precursors [56, 57]. Patients with acute phase schizophrenia had lower HDL and higher LDL levels [58]. Thus, the outcome of this research confirms the same results.

Conclusion: In schizophrenic patients, GM-CSF expression was decreased after antipsychotic treatment for one month and continued the decrease after two months of treatment. GM-CSF expression starts to increase after the two-month treatment and continues increasing to levels of healthy or newly diagnosed schizophrenics after chronic treatment. CBP were not changed. Liver function showed a transient increase in ALP after one and two months of treatment. Kidney function showed a transient decrease in urea after chronic treatment, although these were within the normal range while creatinine was within the normal range during the treatments. LDL was increased after one and two months of treatment and after chronic administration of antipsychotic drugs.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.

Author contributions: All the authors substantially contributed to the conception, compilation of data, checking and approving the final version of the manuscript and agreed to be accountable for its contents.

Ethical issues: Including plagiarism, informed consent, data fabrication or falsification and double publication or submission were completely observed by the authors.

Author declaration: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

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