

Comparison of effect of addition of fluvoxamine or risperidone to clozapine in chronic partially responsive schizophrenic patients on clinical response, QTc interval and Lipid profile

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Abstract

Objective: To study & compare the augmentation effect of addition of fluvoxamine or risperidone in chronic partially responsive schizophrenic patients receiving clozapine on clinical and laboratory parameters.

Methods: A prospective, randomized, parallel, open label 12 weeks study. The schizophrenic patients, aged 20-60 years, who followed the DSM-IV diagnostic criteria and receiving clozapine therapy, showing partial response to the treatment, were recruited and the study was carried out from January 2007 to June 2008. Subjects were randomized into two groups: Group A (n=28): fluvoxamine (25-50mg/day) was added to clozapine (25-200mg/day) & Group B (n=27): risperidone (1-5mg/day) was added to clozapine therapy. The effect of drugs was assessed by PANSS, BPRS scale and ECG and lipid profile were done at 6 and 12 weeks.

Result: There was significant decrease in PANSS and BPRS score in both groups.

Fluvoxamine + clozapine significantly reduced PANSS score as compared to risperidone +clozapine compared to baseline and between 6 and 12 weeks. Risperidone +clozapine prolonged QTc interval (at 12 weeks) and elevated serum TG, VLDL, HDL significantly at 6 and 12 weeks.

Conclusion – Although addition of fluvoxamine and risperidone to clozapine are effective in management of chronic partially responsive schizophrenia on clozapine, fluvoxamine is more effective as well as safer compared to Risperidone when compared for 6 and 12 weeks in these patients.

Keywords: Clozapine, risperidone, fluvoxamine, schizophrenia, QTc

1. Introduction

Antipsychotic polypharmacy is increasingly common, although the evidence of its efficacy from randomized, controlled trials is limited or contradictory. Also there is a risk of exacerbation of side effects, and the cost implications are substantial [1]. Risperidone is, to date, the most extensively documented clozapine augmentation agent. Compared with clozapine, risperidone has greater affinity for D2 and serotonin 5-HT₂ receptors.

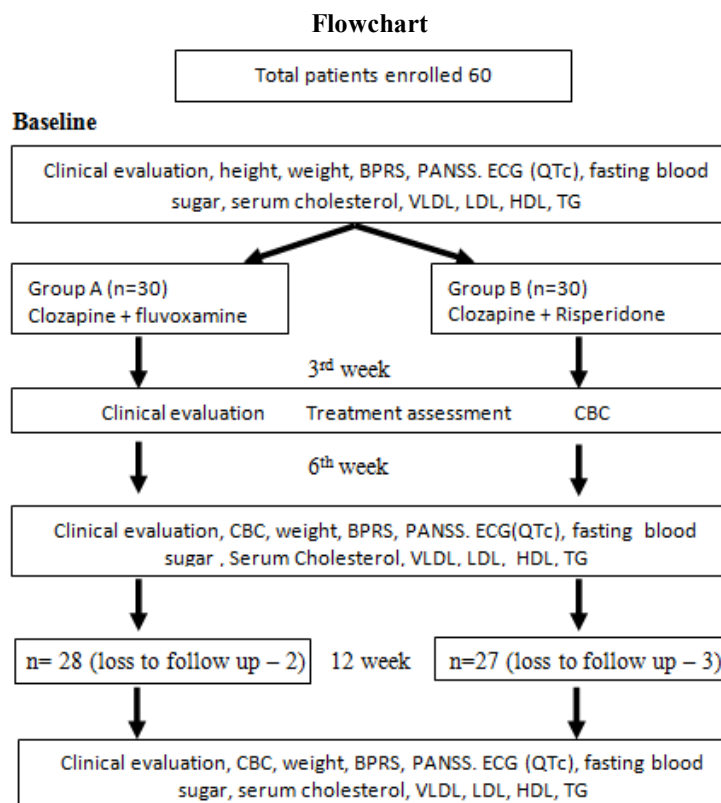
Negative symptoms are core features of schizophrenia that respond poorly to first-generation antipsychotics and present a major obstacle in rehabilitation. Current evidence indicates that at least two SSRIs are needed ameliorate primary negative symptoms in chronic schizophrenic patients treated with first-generation antipsychotics. Selective serotonin reuptake inhibitors (SSRIs) augmentation may be a useful addition to the treatment of schizophrenic patients with persistent negative symptoms. Selection of a better combination and better understanding of these mechanisms can shed light on the pathogenesis of negative symptoms and provide new targets for drug development [2]. Hence we planned the study to compare the effect of addition of fluvoxamine/risperidone to clozapine clinically by evaluating Positive and Negative Symptoms Scale (PANSS) and Brief Psychiatric Rating scale (BPRS) score in chronic partial responding schizophrenic patients and to study the effect of fluvoxamine or risperidone addition to clozapine on ECG and lipid profile in these patients.

2. Material and Methods

A prospective, randomized, parallel group, open label study was conducted in a tertiary care hospital. Eligible subjects were of either sex between 20-60 years of age with i) clinical diagnosis of schizophrenia as per the Diagnostic

and Statistical Manual of Mental Disorder, fourth edition, Text revision (DSM-IV-TR)[3] willing to participate in the study receiving Clozapine and ii) BPRS score more than 40 and showing partial response on PANSS Scale to clozapine therapy. Exclusion criteria were i) Patient with h/o diabetes mellitus, hypertension, hyperlipidemia, arrhythmia, epilepsy & Seizure. ii) Pregnant or nursing women. iii) Women in reproductive age group not using reliable method of contraception. iv) Patient with history of alcohol or drug dependence. The patient recruitment was started only after approval of the Institutional Ethics Committee and written informed consent was obtained from all subjects or their legally acceptable relative (LAR) as applicable. Eligible patients were randomized using computer-generated randomization method with allocation ratio of 1:1 to group A (n=30): fluvoxamine plus clozapine therapy for a period of 12 weeks and group B (n=30): risperidone plus clozapine therapy for a period of 12 weeks. Total duration of study was 18 months.

After initial screening, the data regarding age, sex, past medical history, family history, physical examination, height, weight and clinical examination was recorded in the case report form. Psychiatric rating score was assessed by BPRS and PANSS score.[4,5] ECG(QTc), Laboratory investigations like fasting blood sugar, serum cholesterol, serum triglyceride, serum VLDL, serum LDL and serum HDL were carried out at baseline. Further visits were planned as per flowchart.



Rescue medications (tablet/injection) such as lorazepam 2-8 mg/day, trihexyphenidyl 2-8 mg/day, clonazepam 0.5-2 mg/day, promethazine 25-75 mg/day were available for managing emergency and side effects. General clinical safety was monitored by vigilant follow up of patients for treatment of emergent adverse events; total leukocytes count and differential leukocyte count was done to rule out clozapine induced neutropenia. Reporting of ADR was done as per Pharmacovigilance Programme of India (PvPI).

2.1 Drug administration

The doses of drugs were decided according to clinical condition of patients but in the pharmacological dose range. Patients were instructed to take tablets orally with a glass of water. Group A patients received mean dose of clozapine 109.62 ± 83.60 mg/day (range 25 – 200 mg/day) and fluvoxamine was added in mean dose of 31.25 ± 8.23 mg/day (25 – 50 mg/day). Group B patients received mean dose of clozapine 90.41 ± 46.73 mg/day (range 25 – 200 mg/day) and risperidone is added in mean dose of 2.25 ± 0.81 (range 1 – 4 mg/day).

2.2 Estimation of lipid profile

Serum Total cholesterol, Serum triglyceride (TG), and Serum High density lipoprotein (HDL) were quantitatively estimated using semi autoanalyser, TRANSASIA, ERBA, CHEM-5PLUS [6-8].

Serum VLDL (mg/dL) = {Triglyceride (mg/dL) ÷ 5}[9] and

Serum LDL (mg/dL) = Total Cholesterol (mg/dL) – {HDL+VLDL (mg/dL)}[9]

Calculation of QTc interval = QTc (sec) = QT (sec) ÷ \sqrt{RR} Interval (sec)[10]

2.3 Statistical analysis of data:

Sample size calculation: At the level of significance $\alpha = 5\%$ and power 90%, the sample size of 30 for each group was calculated using pilot study data of 10 patients in each group.

Mean values of change QTc interval, lipid profile, PANSS and BPRS (at baseline, 6 weeks, and 12 weeks) were compared between two groups by using Unpaired 't' test and with-in the groups by Paired 't' test, repeated measures ANOVA. Nonparametric data were compared by using Mann-whitney test, Friedman test with post hoc Dunn's Multiple Comparison test. $p < 0.05$ was considered as statistically significant in all analyses. Graph pad prism 5 was used for analysis.

3. Observations and Results

Both group A and group B were comparable in age, sex and baseline parameters. Five patients, two in group A and three in group B dropped out from the study as they didn't turn to follow up for unknown reasons.

Table 1: Baseline demographic and clinical characteristics of schizophrenic patients

Characteristics	Group A (n = 28)	Group B (n=27)	P value
Age (Years)	37.14 ± 11.46	35.37 ± 11.19	0.5644 [§]
Male : Female ratio	64.28 : 35.71	70.37 : 29.62	
Height (cm)	161.7 ± 9.760	161.0 ± 7.773	0.7890 [§]
Weight (kg)	57.39 ± 10.58	56.74 ± 10.73	0.8214 [§]
Blood sugar level (Random)	113.1 ± 29.53	110.0 ± 24.23	0.6649 [§]
Serum triglyceride (mg/dl)	120.5 ± 21.53	125.6 ± 19.53	0.3698 [§]
Total Cholesterol (mg/dl)	163.9 ± 26.41	165.6 ± 22.47	0.7943 [§]
VLDL (mg/dl)	24.11 ± 4.306	25.11 ± 3.906	0.3698 [§]
LDL (mg/dl)	107.8 ± 44.42	99.00 ± 20.43	0.7490 [#]
HDL (mg/dl)	40.36 ± 7.959	41.48 ± 9.427	0.8925 [#]
PANSS	79.00 ± 13.66	76.56 ± 10.74	0.6611 [#]
BPRS	56.50 ± 11.05	55.78 ± 9.204	0.9194 [#]
QTc interval (sec)	0.3989 ± 0.030	0.4156 ± 0.033	0.0578 [§]

Values are expressed in Mean ± SD. [§]Unpaired t test, [#]Mann-Whitney test applied. VLDL = Very low density lipoprotein, LDL = Low density lipoprotein, HDL = High density lipoprotein, PANSS = Positive and negative symptoms scale, BPRS = Brief psychiatry rating scale

Table 2: Group A: Effects of drugs (Clozapine + Fluvoxamine) after 6 and 12 weeks

Parameters	Group A (n=28)			P value
	0 week	6 week	12 week	
QTc (sec)	0.400 ± 0.029	0.405 ± 0.028	0.406 ± 0.028	0.0613 [#]
TC (mg/dl)	162.266 ± 26.233	162.933 ± 22.996	161.866 ± 23.506	0.7328 [§]
TG (mg/dl)	120 ± 3.813	119.66 ± 22.086	120.11 ± 21.028	0.9592 [§]
VLDL (mg/dl)	24 ± 4.177	23.933 ± 4.117	24.033 ± 4.205	0.9592 [§]
HDL (mg/dl)	40.33 ± 7.684	40.63 ± 6.738	40.866 ± 7.614	0.3119 [#]
LDL (mg/dl)	105.53 ± 43.747	94.06 ± 38.358	98.53 ± 38.567	0.6233 [#]

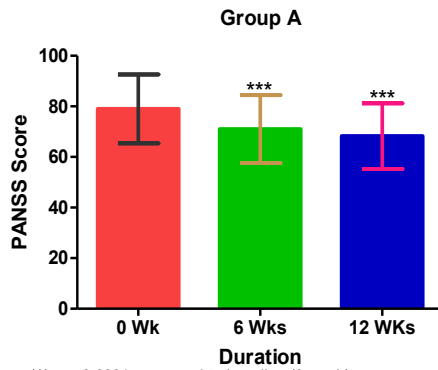
Values are expressed as Mean ± S.D. $p < 0.05$ is considered as a statistically significant. [§] Repeated measures ANOVA, [#] Friedman test applied.

Table 3: Group B: Effects of drugs (Clozapine + Risperidone) after 6 and 12 weeks

Parameters	Group B(n=27)			P value
	0 week	6 week	12 week	
QTc (sec)	0.4156 ± 0.033	0.4181 ± 0.032	0.4233 ± 0.034	0.0005 [§]
TC (mg/dl)	165.6 ± 22.47	168.2 ± 19.97	169.7 ± 26.13	0.2181 [§]
TG (mg/dl)	125.6 ± 19.53	127.4 ± 21.50	132.2 ± 21.77	0.0462 [§]
VLDL (mg/dl)	25.11 ± 3.906	25.48 ± 4.30	26.44 ± 4.353	0.0462 [§]
HDL (mg/dl)	41.48 ± 9.427	42.93 ± 8.458	44.59 ± 9.959	0.0093 [#]
LDL (mg/dl)	99.00 ± 20.43	99.81 ± 18.83	98.67 ± 24.67	0.8940 [§]

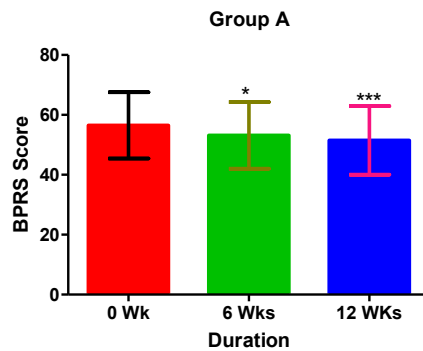
Values are expressed as Mean ± S.D. $p < 0.05$ is considered as a statistically significant. [§] Repeated measures ANOVA, [#] Friedman test applied.

Figure 1 - Within group (Clonazepam + Fluvoxamine) comparison of PANSS score



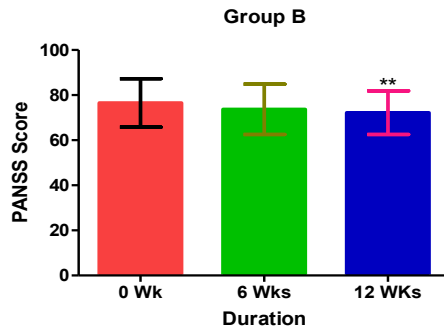
*** p < 0.0001 compared to baseline (0 week).
Friedman test with post hoc Dunn's Multiple Comparison test applied.

Figure 2 - Within group (Clozapine + Fluvoxamine) comparison of BPRS score



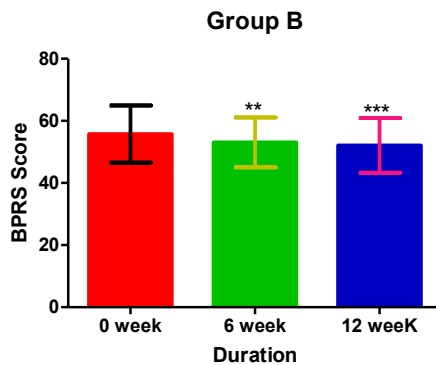
* p < 0.05 & *** p < 0.0001 compared to baseline (0 week).
Friedman test with post hoc Dunn's Multiple Comparison test applied.

Figure 3 - Within group (Clozapine + Risperidone) comparison of PANSS score



** p < 0.001 compared to baseline (0 week).
Friedman test with post hoc Dunn's Multiple Comparison test applied.

Figure 4 - Within group (Clonazepam + Risperidone) comparison of BPRS score.



** p < 0.001 & *** p < 0.0001 compared to baseline (0 week).
Friedman test with post hoc Dunn's Multiple Comparison test applied.

In group A, there was statistically significant improvement in PANSS score at 6 and 12 weeks compared to baseline but in group B, statistically significant improvement is seen only at 12th week compared to baseline (Figures 1 and 3). There was no significant difference seen between groups A & B at 6th and 12th week in PANSS score (Table 5). BPRS score was reduced significantly at 6 & 12 weeks compared to baseline (Figures 2 and 4). When compared between groups, BPRS score was not improved significantly compared to Group B at 6 and 12 weeks (Table 5). QTc was significantly prolonged at 12 weeks in Group B (Table 3). Also serums TG, VLDL, HDL were raised in Group B compared to baseline (Table 3). No changes were observed considering QTc, TC, TG, VLDL, HDL, and LDL in Group A (Table 2).

Table 4: Comparison between the groups at 6th and 12th week in PANSS and BPRS score

Parameter	Duration	Group A (n=28)	Group B (n=27)	P Value
PANSS	6 weeks	71.04 ± 13.39	73.74 ± 11.17	0.2643 ^s
	12 weeks	68.29 ± 12.96	72.22 ± 9.685	0.1733 ^s
BPRS	6 weeks	53.14 ± 11.14	53.07 ± 8.057	0.6426 ^s
	12 weeks	51.50 ± 11.46	52.07 ± 8.797	0.5153 ^s

Values are given as Mean ± S.D. $p < 0.05$ considered statistically significant. ^s Mann-Whitney test is applied to compare between groups A and B.

In the present study, compliance to the drug therapy was also measured. No patient was noncompliant. None of the patients required discontinuation of medication.

4. Discussion

Group A drugs showed sustained improvement in PANSS and BPRS score at 12 weeks in our study. Our results are consistent with Henry Silver *et al* [11], Lammers CH *et al* [12], who reported augmentation of clozapine by fluvoxamine lead to decreased in BPRS score. Also Lu ML, *et al* [13] observed that combined treatment is well tolerated and effective. Clozapine is metabolized through the CYP₄₅₀ 2D6 and 1A2 isoenzyme systems. Fluvoxamine competes for the latter metabolic sites, and it is likely that this interaction produced raised serum clozapine levels in these patients and possibly underlies the clinical improvements and minimal adverse effects [13-15]. The negative symptoms of schizophrenia are associated with dopaminergic hypoactivity in the prefrontal cortex (PFC). Fluvoxamine by increasing dopamine levels in prefrontal cortex area produces a pharmacological picture resembling that of atypical antipsychotics. [16]

Clozapine + Risperidone combination in our study also produced reduction in PANSS and BPRS score in 12 weeks. This is similar to the observations of Taylor *et al* [17], Josiassen *et al* [18] studies. However Yagcioglu *et al* [19], Honer *et al* [20] and Freudenreich *et al* [21] did not find these results may be because they had study duration of 6 weeks. The proposed mechanism for this enhanced clinical efficacy of combining clozapine to risperidone and vice versa is the difference in affinity of the two drugs for brain receptors. Risperidone affinity is related mainly to D₂, 5-HT₂ and α_1 receptors, while clozapine is attached to D₁, D₂ (relatively weak) and D₄, 5HT₂, α_1 and α_2 , muscarinic and H₁ receptors (4, 5). [22,23]

QTc Interval: Group B drugs significantly prolonged QTc interval 12 weeks from baseline but remained within the normal acceptable clinical range.

In metanalysis of Tran *et al* [24] & Harrigan *et al* [25], supports the results of our study. Also, the various studies of Hennessy S and Bilker WB [26], Haddad PM and Anderson IM [27], Stollberger C, and Huber JO [28] mentioned similar observations.

Lipid Profile: The significant rise in serum TG, VLDL and HDL in Group B in our study is supported by Martin A and L'Ecuyer S, that hyperlipidaemia was associated with clozapine compared to typical antipsychotics [29]. Hossein Khalili [30] showed that risperidone had mixed effects on lipid profile. Lu ML *et al* [31] observed that addition of fluvoxamine to clozapine did not have significant effect on body weight, blood sugar & lipid profile, as seen in this study.

5. Limitations

Although, significant efforts have been taken to control for important potential confounders, these efforts are not full proof. Factors such as social class, dietary habits, daily physical workout, alcoholism, smoking, and medical illnesses may have influenced the results of this analysis. However, presence of these confounding factors, in fact represent the actual psychiatric practicing scenario. Another limitation of the present study is that the duration of twelve weeks might be relatively short. This duration of twelve weeks may not have been sufficient enough to allow for more changes in ECG and cholesterol levels to emerge.

6. Conclusion

Addition of fluoxamine and risperidone to clozapine are effective in management of chronic partially responsive schizophrenia treated with clozapine. Fluoxamine is more effective as well as safer to be added to clozapine than risperidone when compared for 6 and 12 weeks. A longer study can reveal more detailed knowledge about efficacy as well as the lipid profile changes, QTc prolongation caused by these drugs.

References

- [1] Procyshyn RM, Thompson B. Patterns of antipsychotic utilization in a tertiary care psychiatric institution. *Pharmacopsychiatry* 2004; 37:12-7.
- [2] Silver H. Selective serotonin re-uptake inhibitor augmentation in the treatment of negative symptoms of schizophrenia. *Expert Opin. Pharmacother* 2004; 5(10).
- [3] Lieberman J.A. – Atypical antipsychotics drugs as a first- line treatment of schizophrenia: a rational and hypothesis. *J Clin Psychiatry*. 1996; 57(11):68-71.
- [4] Kay SR, Opler LA. Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophr Bull* 1987; 13:261-276.
- [5] Woerner MG, Mennuzza S, Kane JM. Anchoring the BPRS-A: an aid to improved reliability. *Psychopharmacol Bull* 1988; 24:112–117
- [6] Tarbutton PN, Gunter CR. Quantitative estimation of serum total cholesterol. *Clin Chem* 1974; 20:724-26.
- [7] Foosati P. Quantitative estimation of serum triglyceride. *Clin Chem* 1982; 28:2077-79.
- [8] Finley PR. Quantitative estimation of serum HDL cholesterol. *Clin Chem* 1978; 24:931-34.
- [9] Rifai N, Warnick GR. Lipids, lipoproteins, apolipoproteins, and other cardiovascular risk factors In: Tietz textbook of clinical chemistry and molecular diagnostics. 4thed. Burtis CA, Ashwood ER, Bruns DE editors, An Imprint of Elsevier, 2006:903-81.
- [10] Goldberger AL. Electrocardiography. In: Harrison's principles of internal medicine, 17th ed. Kasper, DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editor New York: McGraw Hill, 2008;1388-1404.
- [11] Silver H, Kushnir M. Fluvoxamine Augmentation in Clozapine-Resistant Schizophrenia: *An Open Pilot Study. Biol Psychiatry* 1996; 40:671-674.
- [12] Lammers CH, Deuschle M, Weigmann H. Coadministration of clozapine and fluvoxamine in psychotic patients—clinical experience. *Pharmacopsychiatry* 1999; 32(2):76-7.
- [13] Lu ML, Lane HY, Chen KP. Fluvoxamine reduces the clozapine dosage needed in refractory schizophrenic patients. *J Clin Psychiatry* 2000; 61(8):594-9.
- [14] Hermann W. Pharmacokinetic Interactions of Clozapine With Selective Serotonin Reuptake Inhibitors: Differential Effects of Fluvoxamine and Paroxetine in a Prospective Study. *J Clin Psychopharmacol* 1998; 18(1):2-9.
- [15] Olesen, Ole V, Linnet, Kristian. Fluvoxamine-Clozapine Drug Interaction: Inhibition *In Vitro* of Five Cytochrome P450 Isoforms Involved in Clozapine Metabolism. *J Clin Psychopharmacol* 2000; 20(1): 35-42.
- [16] Silver H. Selective serotonin reuptake inhibitor augmentation in the treatment of negative symptoms of schizophrenia. *Int Clin Psychopharmacol* 2003; 18:305–313.
- [17] Taylor CG, Flynn SW, Altman S, Ehmann T. An open trial of risperidone augmentation of partial response to clozapine. *Schizophr Res* 2001; 48:156-8.
- [18] Josiassen RC, Joseph A, Kohegyi E. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 2005; 162:130-6.
- [19] Yagcioglu Anil AE, Kivircik Akded BB. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. *J Clin Psychiatry* 2005; 66(1):63-72.
- [20] Honer WG, Thornton AE. Clozapine alone versus clozapine and risperidone with refractory Schizophrenia. *N Engl J Med* 2006; 354:472–482.
- [21] Freudenreich O, Henderson DC. Risperidone augmentation for schizophrenia partially responsive to clozapine: A double-blind, placebo-controlled trial. *Schizophr Res* 2007; 92:90–94
- [22] Raskin S, Katz G, Zislin Z, Knobler HY, Durst R. Clozapine and risperidone: combination/augmentation treatment of refractory schizophrenia: a preliminary observation. *Acta Psychiatr Scand* 2000; 101:334–336.
- [23] Honer WG, Thornton AE. Clozapine alone versus clozapine and risperidone with refractory Schizophrenia. *N Engl J Med* 2006; 354:472–482.
- [24] Tran, Pierre V. Double-Blind Comparison of Olanzapine Versus Risperidone in the Treatment of Schizophrenia and Other Psychotic Disorders. *J Clin Psychopharmacol* 1997; 17(5):407-418.

- [25] Harrigan EP, Miceli JJ. A Randomized Evaluation of the Effects of Six Antipsychotics Agents OnQTc, In the Absence and Presence of Metabolic Inhibition. *J Clin Psychopharmacol* 2004; 24:62–69.
- [26] Hennessy S, Bilker WB, Knauss JS. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ* 2002; 325:1-5.
- [27] Haddad PM, Anderson IM. Antipsychotic-Related QTc Prolongation, Torsade de Pointes and Sudden Death. *Drugs* 2002; 62 (11): 1649-1671.
- [28] Stollberger C, Huber JO. Antipsychotic drugs and QT prolongation. *Int Clin Psychopharmacol* 2005; 20:243–251.
- [29] Lund BC, Perry PJ. Clozapine use in patients with Schizophrenia and the Risk of Diabetes, Hyperlipidemia, and Hypertention. A claims- Based Approach. *Arch Gen Psychiatry* 2001; 58:1172-1176.
- [30] Khalili H. Effects of Risperidone on Lipid Profile. *Ann Pharmacother* 2007; 41:899.
- [31] Lu ML, Lane HY, Lin SK. Adjunctive fluvoxamine inhibits clozapine-related weight gain and metabolic disturbances. *J Clin Psychiatry*. 2004 Jun; 65(6):766-71.