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Research Article

Perphenazine Versus Trifluoperazine Versus Aripiprazole Versus Quetiapine in Treatment of Non-Affective Acute Psychosis: A Blind, Randomized - Controlled Clinical Trial

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Abstract

Objective: The main goal of current design is to compare the efficacy of four antipsychotics drugs in treatment of non-affective acute psychosis. In our study, we compared four psychotropics: Aripiprazole, Perphenazine, Quetiapine and Trifluoperazine. Additionally, we compared some of the side effects accompanied with these drugs.

Methods: In current blind, randomized-controlled clinical trial (RCT), we collected a total number of 90 hospitalized acute psychosis diagnosed patients via convenient sampling method; subsequently they were assigned into four groups Aripiprazole: (24 patients), Perphenazine: (22 patients), Trifluoperazine: (21 patients), and Quetiapine: (23 patients). The drugs were administered among four groups of patients during 6 weeks period. Aripiprazole was administered in 5 dosage (10 mg, 15 mg, 20 mg, 25 mg, 30 mg), Perphenazine in 3 dosage (24 mg, 32 mg, 40 mg), Quetiapine in 6 dosage (300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg) and Trifluoperazine in 3 dosage (15 mg, 20 mg, 25 mg), during 21 days. The positive and negative symptoms scale (PANSS) was assessed in the first and the last day of the trial. Additionally we screened and recorded some side effects of these drugs in 21 days period.

Results: According to results of current study, it was concluded that all of these drugs could efficiently downgrade the severity of symptoms in acute psychosis. All four drugs reduced positive, negative and general symptoms of non-affective acute psychosis. Although, the difference between drugs was not statistically meaningful. Furthermore, with respect to side effects (constipation, orthostatic-hypotension, dystonia, tremor, parkinsonism, akathisia and cardiac-problems) of our target drugs, again, no statistically meaningful difference was noticed. Although number of patients treated with Perphenazine and Trifluoperazine (FGA) was more than patients treated with Aripiprazole and Quetiapine(SGA).

Conclusion: With respect to marginal differences with similar studies, study on larger sample pool via long-term follow up is advised in future endeavors.

Keywords: *Aripiprazole; Non-Affective Acute Psychosis; Perphenazine; Positive and Negative Symptoms Scale; Quetiapine; Trifluoperazine*

Introduction

Psychosis is defined as a psychological condition accompanied by impairment of thoughts, idiosyncratic emotional reactions and problematic social communications. This spectrum of malady often tampers with the real-thinking functioning. Orthodoxly psychosis manifestation involves both hallucination and delusion [1]. Fitting and impeccable timing in intervention is correlated with elevated therapeutic results and would obstruct further problems [2]. Chlorpromazine as renaissance in treating psychosis was introduced 1952 [3]. Second generation antipsychotics (SGAs) have been used in clinical setting since 1990; this group of drugs is serotonin-dopamine receptors antagonist. The leading psychotropic of this group was Clozapine following by Risperidone, Olanzapine, Quetiapine, Ziprasidone

and Aripiprazole in late years [4]. SGAs are considered as gold-standard modality comparing to First Generation Antipsychotics (FGAs) in management and reduction of positive and negatives symptoms of psychosis, however there are still some controversies regarding clinical superiority of SGAs over FGAs; advocates of SGAs postulate that this group of drugs have less side effects and they are more efficient with respect to drug resistant patients. Admittedly, latter group are accompanied with less relapse rate and hospitalization duration [4]. Concrete suggestion with respect to gold-standard modality option among antipsychotics is still lacking. The novel aim of current design is to compare the efficacy of Perphenazine versus Trifluoperazine versus Quetiapine versus Aripiprazole in treatment of non-affective acute psychosis. Optimistically, the results would benefit both clinicians and patients by optimizing to therapeutic process. By optimizing therapeutic process, we aim to choose the best treatment choice for patients; this would save patients from undergoing frustrating road of experiencing various drugs and enduring various financial and physical difficulties. Very few RCTs have compared these four drugs in Iran. In recent years, mushrooming trend in production and using of neuroleptics further to uncertain results of different studies, we aimed to compare the efficacy of these four drugs in treatment of acute phase of non-affective psychosis.

Psychosis and Schizophrenia

Between DSM-V numerous disorders and maladies, psychosis and more precisely schizophrenia is one of the most baffling disorders and it shares great importance among clinicians and consequently it calls for more attention because of its collateral damages for patient, health system and society. Apart from financially imposing role of schizophrenia on household and health sectors, schizophrenia includes widespread continuum of cognitive, social and emotional problems in personal level, and would impose great deal of psychological distress to the caregivers [1].

Bleuler was the first physician who coined the term Schizophrenia. Emil Kraepelin was the first clinician who explicitly categorized schizophrenia as a disorder; he coined the concept youth psychosis due to early onset of this disorder [2].

Schizophrenia is a lingering, devastating mental disorder that interferes with thinking process, emotions and behaviors of afflicted individuals; afflicted individuals usually loose their touch with reality testing. Fortunately, schizophrenia is not as common as other mental disorders such as depression or anxiety, however level of debilitation of the symptoms is extremely high in most cases.

Recent literatures have postulated a modification of some broadly cited, however inadequately supported by proof, dimensions of schizophrenia epidemiology. The first misjudgment is the notion that schizophrenia maintain universal incidence within various cultures and countries. The second is the creed that schizophrenia has same prevalence in males and females. All in all, these viewpoints could be hypothesized as schizophrenia is an equalitarian disorder, and schizophrenia is an unique disorder. It is confusing that these two interconnected views are usually quoted as support regarding biological origin of schizophrenia, while in medicine most diseases do vary across cultures, countries, and gender [3].

Schizophrenia is a disorder of the brain with multi-roots and causality, chronicity, and different symptom expressions. Antipsychotics are goal standard treatment approach in the therapy of schizophrenia and anxiolytics, antidepressants, antiepileptics are only adjuvants with temporary use. Former studies, do not offer enough evidence regarding treatment of cognitive symptoms, and the new antipsychotics may improve the negative symptoms moderately. The decrease and inhibition of positive symptoms is attainable with the established selection of antipsychotics. The typical-atypical categorization is an obsolete concept since there are pharmacological differences not only between the two groups but within the groups as well. There are no suggestive dissimilarities among the antipsychotics with respect to efficiency but their side effect profiles tend to vary.

Drug choice is influenced by various factors such as psychological state, medical conditions, comorbidity condition and specific characteristics of drugs such as pharmacodynamic sand pharmacokinetics. The next principal consideration is the adjustment of the dose. Dose adjustment depends on multiple factors such as patient's somatic conditions and pharmacological factors, such as absorption, activity of metabolizing enzymes, function of the blood-brain barrier. Lacking aforementioned data would force clinician to optimize the dose by considering clinical response. The switch of a drug is vital if it is unsuccessful or causes severe side effects.

Throughout roller-coaster course of schizophrenia, patient undergoes various unfavorable states such as depression, anxiety, aggression. In this sense, the treatment would target symptoms with pharmacotherapy, but the risk/benefit ratio of these therapies should be precisely noticed. Apart from pharmacotherapy, patients would benefit from psychotherapeutic interventions and/or social therapy, however due to dominant biological etiology of this malady it is unlikely to reach promising clinical outcome without efficiently adherence to pharmacotherapy. Essential points not to be neglected are the patient's well-being and the functionality score, in addition to suitable choice of pharmacological agents and the right drug therapy [4,5].

All in all, in Iran we did not find any similar study; hence, notifying aforementioned dilemmas, it appeared vital and plausible to conduct this study.

Materials and Methods

In current blind, randomized-controlled clinical trial (RCT), we chose 108 patients (who were reduced to 90 patients later on) via convenient sampling method from a psychiatric Hospital (Sari, Iran); subsequently we assigned them into four groups (Perphenazine, Trifluoperazine, Aripiprazole, Quetiapine) for 6 weeks intervention via aforementioned drugs. We chose aforementioned drugs due to high frequency of administration of them in psychiatric setting in management of psychosis, and because we aim to assess if different receptor binding profile is related to different clinical outcome or not?

Inclusion criteria

- Age range between 18 - 50 years;
- All four groups were matched according to gender and age;
- Inpatients in psychiatric Hospital;
- Diagnosed according to DSM-5 criteria for psychosis spectrum diagnoses (non-organic, non-drug-induced, non- affective): Schizophrenia, delusional disorders, shared psychotic disorders, Schizoaffective disorders;
- Clinical indication regarding of antipsychotic pharmacotherapy;
- Psychotic symptoms (scoring ≥ 4);
- Existence of the following PANSS items: delusions, conceptual disorganization, hallucinations, grandiosity, suspiciousness/persecution, or unusual thought content; as well as a total PANSS score > 60 points;
- Antipsychotic-naïve/limited exposure (no use antipsychotics orally 6 weeks prior to study and regarding long acting, antipsychotics this period defined as 8 weeks);
- Acquiring written informed consent forms from caregivers (Due to severity of symptoms in acute phase of psychosis, consent forms could not be obtained from patients, however the procedure of study was explained to them completely).

Exclusion criteria

- Drug-induced psychosis;
- Organic psychosis caused by general medical condition;
- Chronic somatic/neurological condition;
- Existence of history of severe head trauma (according to physical and neurological examinations) based on physical and neurological examinations;
- Noticing abnormal laboratory tests (CBC, FBS, BUN, Creatinine, ALT, AST, Alkaline Phosphatase, U/A and also ECG);
- Pregnancy or lactation;
- Substance dependency (based on DSM-5 and laboratory tests) within the last year;
- Consuming any other drugs even in PRN situation during study period (except biperiden or trihexyphenidyl if needed);
- Electro Convulsive therapy (ECT) based on attending physician order.

We conducted current study in accordance with the declaration of Helsinki and good clinical practice according to international conference on harmonization guidelines. The interventions were blinded to participants, caregivers, statisticians, and conclusion drawers. The patients were administered, Aripiprazole in 5 dosage (10, 15, 20, 25, 30), Perphenazine in 3 dosage (24, 32, 40), Quetiapine in 6 dosage (300, 400, 500, 600, 700, 800) or Trifluoperazine in 3 dosage (15, 20, 25), in a 6 weeks period. The positive and negative symptoms scale (PANSS) was done in the first and the last day of the trial.

We decided to conduct current study among sample of 90 patients; this number was decided according to G-Power software considering potency of 80. Considering a probability of exclusion under any circumstances and due to unpredicted problems during the study, in first step 108 patients were chosen for current study. The patients were allocated into four groups via random numbers nature and rand-between function.

We used Positive and negative symptoms scale (PANSS) in order to measure the severity of negative and positive and general psychiatric symptoms; PANSS measures 7 negative symptoms, 7 positive symptoms and 14 general psychopathologic symptoms. Each symptom is scored between 0 - 7 based on severity. Ghamari., *et al*. 2010 confirmed validity and reliability of this Scale in Iranian population [6].

Penultimately, participants were assessed again by PANSS. Throughout the study Electrocardiography (ECG), blood pressure, pulse, body mass index, abdominal circumference, laboratory test results were obtained weekly from all participants.

Finally, obtained data were analyzed via SPSS software version 19. We used Mean and standard deviation (SD) regarding quantitative variables such as age and PANSS, regarding qualitative variables, distribution frequency chart was used.

Effectiveness of the drugs was measured via Analyze of Variance with repetitive measurement of Chi-square and one-way Analyze of Variance with Bonferoni post-test. When cofounding variables were not the same among groups, we used Generalized Estimated Equations (GEE). In our design, P-value less than 0.05 were considered significant.

Tools

PANSS (Positive and Negative Symptoms Scale)

Initially, PANSS was created based on a schizophrenia categorization into two categories of positive/negative symptoms. The positive symptoms are productive symptoms, whereas the negative syndrome manifests the deficit symptoms. This distinction becomes handy for treatment utilization and developing treatment plans; as clinicians would target specific group of symptoms that patient is suffering from. It also is being frequently used regarding assessment of psychotropic in clinical trials; to decide which groups of symptoms are being affected by them. In Iran, Ghamari and colleagues confirmed validity and reliability according to Iranian population pool [6,8].

Results

In this section, for describing characteristics of our sample, initially we used descriptive statistics and subsequently we applied inferential statistics regarding accepting or rejecting the hypothesis of our study.

We conducted this study in order to assess efficacy of four neuroleptics in treatment of non-affective acute psychosis. One hundred eight patients were included in this study. Seven patients discharged by attending physician before 3 weeks so, were excluded from our study; five patients needed ECT according to comments of attending physician, they were excluded from the study too. Furthermore, six patients received PRN. Finally, study was conducted among 90 patients with non-affective acute psychosis. A total number of 90 hospitalized patients with the diagnosis of acute psychosis were selected via convenient sampling method. The positive and negative symptoms scale (PANSS) was assessed in the first and the last day of the trial.

Data regarding gender distribution can be notice on figure 1.

In order to compare gender distribution among four groups we used chi-square test and we didn't find any meaningful difference (P-value = 0.283). Details can be noticed on table 1.

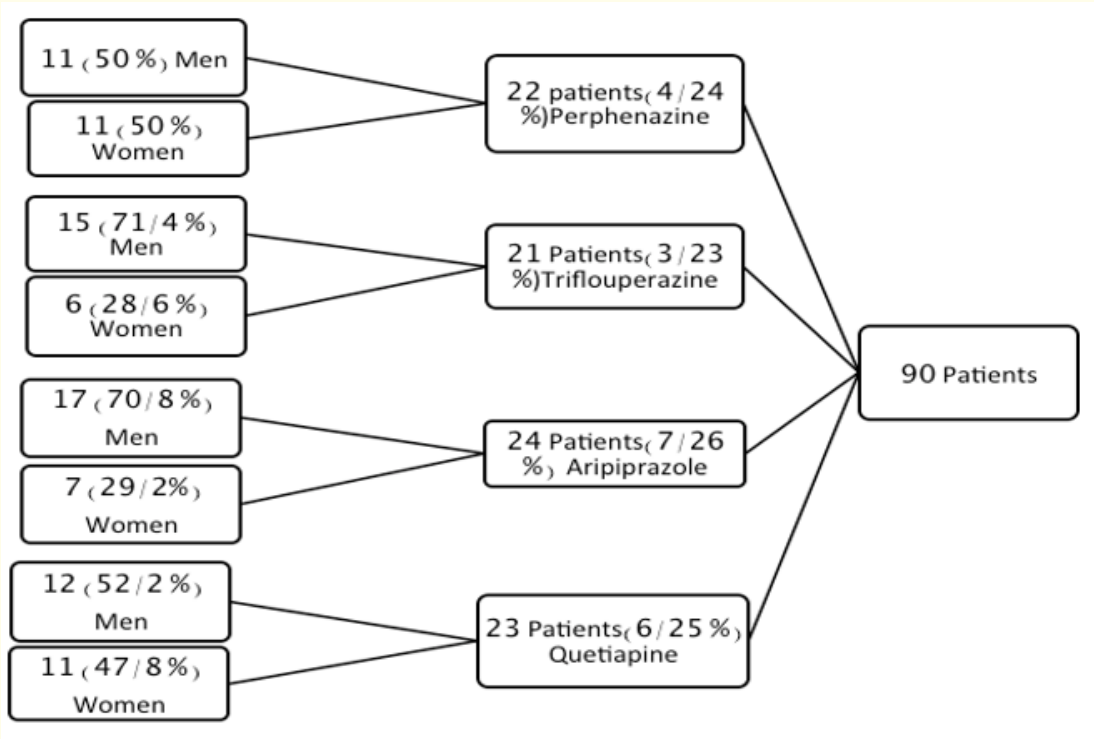

Figure 1: *Data regarding gender distribution.*

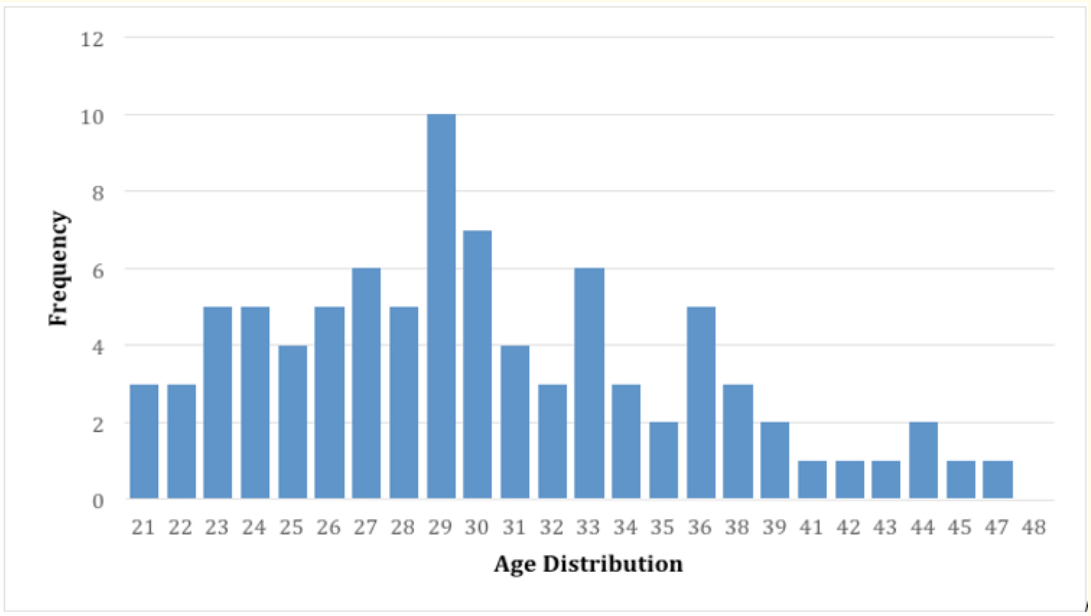

Figure 2: *Age distribution*

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	3.811[a]	3	.283
Likelihood Ratio	3.843	3	.279
Linear-by-Linear Association	.016	1	.898
N of Valid Cases	90		

Table 1: *Comparing Gender distribution among four groups.*

With respect to comparing of mean age among four groups we conducted Kruskal Wallis Test and we did not mention any meaningful difference among groups (P-value = 0/041).

	Age
Chi-Square	8.275
df	3
Asymp. Sig.	.051

Table 2

Based on duration of disease, patients varied between 1 - 16 months. Data can be noticed on table 3.

	Duration of illness
Chi-Square	7.350
df	3
Asymp. Sig.	.062

Table 3

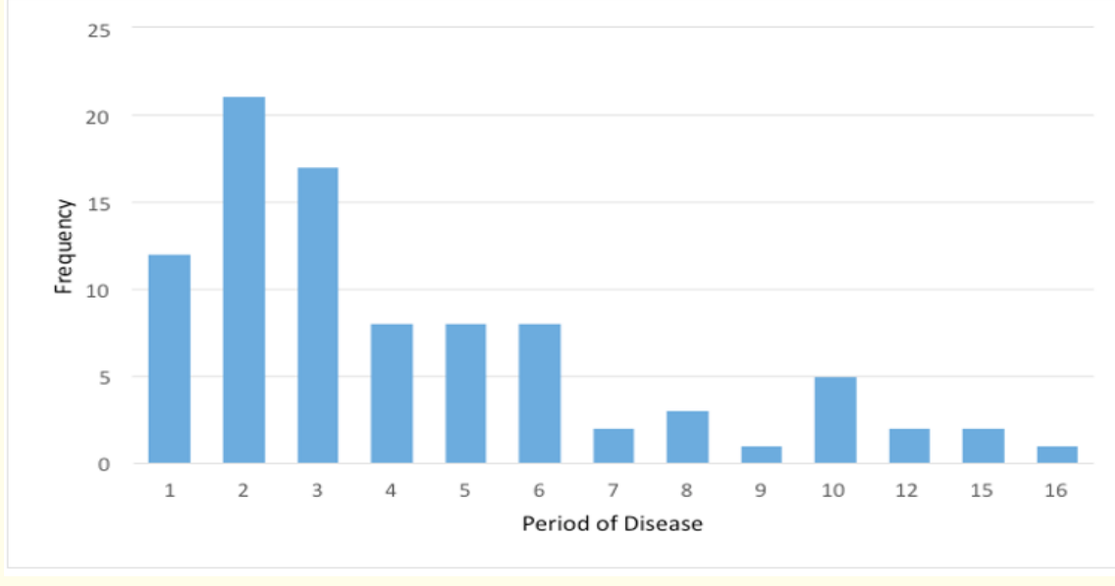

Figure 3: *Duration of disease.*

With respect to comparing of duration of disease among four groups we conducted Kruskal Wallis Test and we did not mention any meaningful difference among groups.

The drugs were administered among four groups of patients; Aripiprazole in 5 dosage (10, 15, 20, 25, 30), perphenazine in 3 dosage (24, 32, 40), Quetiapine in 6 dosage (300, 400, 500, 600, 700, 800) or Trifluoperazine in 3 dosage (15, 20, 25), in a 3 weeks period.

Following table illustrates data regarding pretest and posttest of PANSS (Positive, Negative and General).

PANSS	Drug	Pre-Test	Post-Test
Positive	Perphenazine	28/7 ± 73/32	22/4 ± 00/12
	Trifluoperazine	74/5 ± 00/26	49/5 ± 24/9
	Aripiprazole	44/8 ± 75/32	26/6 ± 38/12
	Quetiapine	61/7 ± 22/27	68/6 ± 09/10
Negative	Perphenazine	59/10 ± 59/25	29/8 ± 18/12
	Trifluoperazine	23/10 ± 52/27	96/7 ± 62/12
	Aripiprazole	47/7 ± 17/24	35/6 ± 17/12
	Quetiapine	39/9 ± 87/24	25/7 ± 74/10
General	Perphenazine	39/24 ± 59/108	72/12 ± 23/37
	Trifluoperazine	01/23 ± 33/101	16/11 ± 33/35
	Aripiprazole	17/23 ± 25/105	81/10 ± 42/35
	Quetiapine	80/18 ± 96/99	69/8 ± 30/33
Total	Perphenazine	13/37 ± 90/166	88/21 ± 40/61
	Trifluoperazine	82/28 ± 85/154	62/18 ± 19/57
	Aripiprazole	13/34 ± 16/162	60/20 ± 95/59
	Quetiapine	02/30 ± 04/152	34/18 ± 13/54

Table 4: *Pretest and Posttest Scores of PANSS.*

Data regarding side effects (constipation, orthostatic-hypotension, dystonia, tremor, parkinsonism, akathisia and cardiac-problems) can be mentioned on.

Inferential statistics

Following table shows data regarding efficacy of aforementioned drugs.

According to table 6, all four drugs substantially reduced the scores of general symptoms of PANSS. However, and the difference regarding four drugs was not statistically meaningful. According to table 6, all four drugs substantially reduced the scores of positive symptoms of PANSS. However, and the difference regarding four drugs was not statistically meaningful. According to table 6, all four drugs substantially reduced the scores of negative symptoms of PANSS. However, the difference regarding four drugs was not statistically meaningful. According to table 6, all four drugs substantially reduced the total score of PANSS. However, the difference regarding four drugs was not statistically meaningful.

In order to assess difference of side effects among four drugs, chi-square test was used. Details can be noticed on table 7.

With respect to side effects of drugs, no statistically meaningful difference was observed among four drugs. However, number of patients treated with FGAs (perphenazine and trifluoperazine) was more than patients treated with SGAs (aripiprazole and quetiapine). It appears plausible that no statistically difference between drugs may stem from rather small statistical sample. Furthermore, some patients tend to manifest side effects in a longer period of time.

Drug	Side effects	Number
Trifluoperazine	Constipation	2
	Orthostatic Hypotension	3
	Acute Dystonia	1
	Tremor	1
	Parkinsonism	2
	Akathisia	1
	Cardiac Effect	-
Aripiprazole	Constipation	-
	Orthostatic Hypotension	2
	Acute Dystonia	-
	Tremor	-
	Parkinsonism	2
	Akathisia	2
	Cardiac Effect	1
Perphenazine	Constipation	1
	Orthostatic Hypotension	1
	Acute Dystonia	1
	Tremor	2
	Parkinsonism	-
	Akathisia	1
	Cardiac Effect	1
Quetiapine	Constipation	-
	Orthostatic Hypotension	1
	Acute Dystonia	-
	Tremor	1
	Parkinsonism	-
	Akathisia	1
	Cardiac Effect	1

Table 5: *Side-effects of drugs.*

Dependent Variable	Source	Sum Square	DoF	Mean Square	F	Meaningfulness	Eta Square
General Symptoms-Post Test	General Symptoms- Pre Test	288/56	1	288/56	949/149	000/0	638/0
	Groups	286/0	3	095/0	z254/0	858/0	009/0
	Error	907/31	85	375/0			
	Total	000/89	90				
Positive Symptoms-Post Test	Positive Symptoms- Pre Test	789/44	1	789/44	074/99	000/0	538/0
	Groups	219/0	3	073/0	162/0	922/0	006/0
	Error	000/89	85	452/0			
	Total	000/89	90				
Negative Symptoms-Post Test	Negative Symptoms- Pre Test	626/61	1	626/61	614/198	000/0	700/0
	Groups	098/1	3	366/0	179/1	322/0	040/0
	Error	374/26	85	310/0			
	Total	000/89	90				
Total Score	Total Score- Pre Test	025/26447	1	025/26447	301/291	000/0	774/0
	Groups	192/56	3	366/0	206/0	892/0	040/0
	Error	098/7717	85	789/90			
	Total	000/89	90				

Table 6: *Results of single variable covariance.*

Perphenazine		Drug				Total
		Trifluoperazine	Aripiprazole	Quetiapine		
Side Effects	Yes	10	7	7	4	28
	No	12	14	17	19	62
Total		22	21	24	23	90

	Value	Df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.223[a]	3	.238
Likelihood Ratio	4.319	3	.229
Linear-by-Linear Association	4.050	1	.044
N of Valid Cases	90		

Table 7: *Results of Chi-Square Tests with Respect to four drugs side effects.*

Discussion and Conclusion

In current study, we aimed to determine the efficacy of Perphenazine versus Trifluoperazine versus Aripiprazole versus Quetiapine in management of non-affective acute psychosis. According to results of current study, we can postulated that all of these drugs can significantly reduce the severity of symptoms of acute psychosis; the differences in reducing total, positive and negative scores were not significant and all drugs had more less same efficacy. Our results are consistent with results of the study of Potkin and Colleagues [8]. In their study, they study acute psychotic patients who were in acute phase of the disorder and the intervention period was 6 weeks. This may justify that efficacy of these four drugs in reducing positive and negative symptoms in different kind of psychosis with short intervention period are similar. Our findings are concordant to result of the study of Yan Li and colleagues [9,10]. They conducted their study during 6 weeks period, no significant difference was noticed with respect to alleviating psychotic symptoms with Quetiapine and Aripiprazole and Chlorpromazine on a daily dosage. Because of administration of Quetiapine in higher dose in Yan's study, we cautiously can postulate that efficacy of both drugs may differ in each patient and adequating dosage with chlorpromazine is not always necessary.

Y-hua and Collageues (2012) studied schizophrenic during 8 weeks period; patients didn't demonstrate meaningful difference in responding to Quetiapine and Resperidone [9], and the result is similar to the result of present study. In aforementioned study, all participants were women and this can be inferred that we have equalitarian approach regarding both sexes. Additionally, with respect to superior effectiveness of Aripiprazole in reducing general symptoms comparing to Quetiapine, which was not resulted in current study, result is as same as the results of other studies [10-12]. Although, for understanding causes of similarity of Aripiprazole and Quetiapine effects in reducing positive and negative symptoms and differences in general scores, further investigations may be required. In Komossa and Colleagues' review study in 2011 was conclude that Quetiapine was less effective than Risperidone and Olanzapine in controlling the symptoms of psychosis [14]. In current study, effectiveness of Perphenazine, Trifluoperazine, Aripiprazole and Quetiapine in reducing acute psychotic symptoms was equal and the difference in results of two studies maybe due to difference in research's method, age criteria and genetic background. Komossa and colleagues again postulated in another study that Risperidone is more effective than Quetiapine in reducing PANSS [12]. In our study, the results are not consistent with the results of aforementioned study. This dilemma may need further pharmacological and pathophysiological researches.

Zhong and Colleagues (2008), conducted 8 weeks study among schizophrenic patients with daily dose of 525 mg Quetiapine and 5.2 mg perphenazine; it was concluded that the group treated by quetiapine showed more decreased positive symptoms [13]. In current study, mean dose of Quetiapine was less than mean dose of perphenazine and this may explain the same effectiveness of FGAs and SGAs. It appears plausible that although each patient may be treated with different dose of drug but mean dose for most patients is being affected by function of most dopaminergic receptors and partially serotoninergic receptors. In other study conducted by Johnson, decrease in PANSS for Quetiapine was more and faster in comparing other drugs [14]. It seems that, one of the differences of Johnson's study with

current study is difference of PANSS score in patients by baseline point of the study. In Johnson's study PANSS score was 74 and in our study, the score was 91.5 by the time we started the study. Furthermore, duration of treatment and follow-up of the patients in Johnson's study was 2 years, which means that that study covered both acute and residual phase of the disorder, but in our study, we only covered acute phase.

Finally in another study conducted by Moosavi and Colleagues (2015), they compared efficacy of Risperidone and Quetiapine in treatment of Acute Psychosis. According to their results, no significant difference found between two groups in decreasing positive and negative sub-scores in the PANSS. Risperidone was superior to Quetiapine in decreasing the PANSS general psychopathology sub-scores and total score ($p < 0.05$) [15].

Limitation

1- The trial was with patients undergoing acute treatment (phase I). Potentiation (phase II) and maintenance (phase III) (long-term treatment) is an issue of great importance and should be evaluated further through more in-depth studies given that psy chosis is a chronic disease.

2- It is advisable to conduct a study in larger sample pool.

3- Follow-up sessions should be conducted in future studies.

Declaration of Interest

None.

Acknowledgement

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Authors Contributions

MBM designed the study. MBM and SMM collected clinical data. MH helped us with respect to conducting statistical analysis. MBM drafted the manuscript. All authors read and approved the manuscript.

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