

## Low Dose Celecoxib Combined with Clozapine for Treatment of Schizophrenia: A Double Blind Randomized Clinical Trial

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### Abstract

**Introduction:** Higher levels of pro-inflammatory cytokines in schizophrenia have suggested that dysfunctions of the immune system may play a role in this disabling condition. The current study was performed to discover if low dose celecoxib combined with clozapine may improve symptoms of schizophrenia or not.

**Methods:** In a double-blind randomized clinical trial, 40 patients with non-treatment resistance schizophrenia were allocated into two groups. The experimental group received flexible and low dose clozapine plus 200 mg/day of celecoxib for 4 weeks, while the control group received clozapine plus placebo. Experimental and control groups were similar in terms of age, gender, clozapine mean dosage and severity of schizophrenic symptoms at baseline. Main outcomes were severity of schizophrenia symptoms measured by the Positive and Negative Syndrome Scale (PANSS) at baseline followed by the second and fourth weeks.

**Results:** Although both groups experienced significant improvement in all PANSS sub-scales in the second and fourth weeks ( $P < 0.001$ ), the differences between the two groups did not reach significance ( $P > 0.05$ ).

**Conclusion:** Our findings did not support the findings of prior studies that report a significant effect for celecoxib combined with atypical antipsychotics. Such inconsistency may be due to statistical power, drug interactions between clozapine and celecoxib, and the low dose of celecoxib used in this study. Future research is needed on the role of anti-inflammatory medications as add-on treatments for schizophrenia.

**Keywords:** Celecoxib, Clozapine, Schizophrenia, Randomized Controlled Trial

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### 1. Introduction

Schizophrenia is a common catastrophic psychiatric disorder affecting almost all the aspects of personal, familial and social life. Since the available treatments are not sufficient enough [1], the recent approach is on its basic etiology and immune dysfunctions are most accused. A great deal of research has suggested that inflammatory cytokines and Microglial activation play an important role in the development of schizophrenia, as well as many other psychiatric disorders [2, 3]. Microglia, which are the main CNS immune cells, produce free radicals and pro-inflammatory cytokines even in minor pathological changes of CNS [3].

Sirota and colleagues indicated an enhanced level of IL-1, TNF- $\alpha$  and IL-3 in patients with schizophrenia [4, 5]. Licino et al showed that cerebrospinal fluid (CSF) level of IL-2 is higher than normal in patients with schizophrenia not receiving psychotropic agents [6]. Then, McAllister et al claimed that the enhancement rate of IL-2 in these patients is related to the frequency of recurrence and prognosis [7]. Muller et al showed that soluble receptor of IL-6 increases in CSF and serum of patients [8]. Also, Kammen et al declared

that IL-10 is involved in their behavioral disorders [9]. Further research showed that type 1 and type 2 immune systems are imbalanced in these patients. Exactly, type-2 system is activated, while type-1 is blunted [10].

Enhancement of pro-inflammatory cytokines in the central nervous system (CNS) results in the cognitive disturbances, perhaps mediated by the cyclo-oxygenase-2 (COX-2) enzyme [11], interacting with acetylcholine, 5-hydroxytryptamine, glutamate and prostaglandin E2 [12]. COX-2 enzyme may be involved with schizophrenia through some probable ways. It is found in neurons [13], and can be activated by some cytokines (such as IL-2, IL-6 and IL-10) which have an important role in the development of schizophrenia [14-17]. On the other hand, it is probable that the interference of COX-2 with the functions of glutamate receptors in hippocampus and amygdale is responsible for the development of this disease [18].

Based on the hypothesis of the dysfunctions of the immune system, immune-modulatory medication may reduce the symptoms of schizophrenia. Recent clinical trials of pharmacotherapy in schizophrenia have shown that co-administration of antipsychotic and anti-inflammatory

drugs have superior beneficial effects comparing with outcomes of using antipsychotic drugs alone [19].

Celecoxib is a selective inhibitor of COX-2 enzyme, approved for the treatment of osteoarthritis [20]. It is permeable in CNS and has been beneficial in some neurologic disorders, such as Alzheimer's disease [18, 21]. Rebalancing the type-1 and type-2 immune responses, it probably decreases the production of pro-inflammatory cytokines [10, 22]. Celecoxib has been effective on animal models of schizophrenia. In a study, the injection of the epidermal growth factor (a molecule that is thought to be responsible for the development of schizophrenic symptoms) into striatum of rats, increased COX-2 expression and induced behavioral impairments. Then, the administration of oral celecoxib (10 mg/kg) normalized the metabolism of dopamine and, again, ameliorated those behavioral impairments [23]. In the recent decade, some controlled clinical trials were conducted concerning the benefits of COX-2 inhibitors in schizophrenia and suggested that celecoxib, as an add-on to atypical antipsychotics, particularly risperidone, is capable to reduce the symptoms of schizophrenia [14, 22, 23]. However, there were some inconsistent results, as well [24, 25].

In order to achieve the best clinical efficacy and minimal side effects of most antipsychotics, there is a narrow therapeutic window of 65-78 % D [2] receptor blockade, but clozapine do not have that therapeutic window and makes sub-threshold levels of D [2] blockade [26]. However, several studies indicate that patients with schizophrenia who are resistant to other antipsychotics may be treated successfully by clozapine [26-29]. Some studies demonstrate that clozapine has immune-modulatory activities [28]. Risperidone, clozapine and COX-2 enzyme affect serotonergic and cholinergic receptors in different ways [12, 27, 29, 30]. The Clozapine effect on serotonin (5-HT) receptors has a major role in the efficacy and tolerability of clozapine and it is important in amelioration of psychosis and cognitive impairment [31]. A proportion of patients with schizophrenia require clozapine therapy and this drug is different from the other atypical antipsychotics in some aspects. Furthermore, the role of anti-inflammatory drugs such as celecoxib have been distinguished in several studies.

The present study was performed to assess the effect of low dose celecoxib add-on to clozapine for the treatment of patients with schizophrenia.

## 2. Methods

### 2.1. Design and Setting

This double-blind randomized clinical trial (phase 3) -approved by the ethics committee of Mashhad University of Medical Science, enrolled 40 patients with schizophrenia admitted in Ibne-e-Sina psychiatric hospital of Mashhad city, northeastern Iran, were selected in 2006.

### 2.2. Participants

The inclusion criteria was the diagnosis of schizophrenia based on the DSM-IV criteria by two psychiatrists and treatment resistance schizophrenia (based on research trials, 1-3

trials that used adequate doses of antipsychotic drugs, each lasting for more than 4-6 weeks, have failed to reduce positive symptoms sufficiently) [32]. The exclusion criteria included the use of any oral antipsychotic except clozapine since the last week, use of long acting antipsychotics since the last month, use of other psychotropic medications such as antidepressants and mood stabilizers (Biperidine/PRN for extrapyramidal complications was exceptional), severe drug side effects and the release of the patients from the hospital before the end of the experiment.

### 2.3. Process

After providing the necessary explanation about the project for the patients' protectors by psychiatrists, an informed consent was signed by the protector of each patient. Then, Demographic data was recorded.

Participants were randomly divided into 2 groups. The experimental group received flexible dosages of clozapine (based on clinical response) Leponex from Novartis company plus 200 milligrams of celecoxib from Abidi company per day in 2 divided doses for 4 weeks, while the control group received flexible dosages of clozapine (Leponex) plus placebo. We preferred a period of 4 weeks, because the majority of patients got a considerable improvement in 4 weeks and persisted to be released from the hospital. During these 4 weeks, 5 patients due to their family's decision for early discharge from the hospital, were excluded.

Low dosages of celecoxib (200 mg/day) in comparison with 400 mg/day in the similar study [14] was cautiously preferred, because there was not any research prescribing the combination of clozapine and celecoxib in human beings before this study and adverse drug interactions were not completely predictable. Also, evidence has suggested that COX-2 inhibitors enhance the probability of seizure [33], which is a side effect of clozapine too. Moreover, a study has shown a side effect of auditory hallucination for celecoxib [34]. Therefore, in the present study, we agreed on 200 mg/day of celecoxib.

### 2.4. Outcome

Main outcome was severity of schizophrenic symptoms evaluated by the positive and negative syndrome scale (PANSS) test [35]. The PANSS consists of 30 main questions (7 questions for positive symptoms, 7 questions for negative symptoms and 16 questions for general psychopathology). The potential score of each was between 1 (absence of symptom) to 7 (excessive symptom), thus the total PANSS score ranges from 30 to 210. Higher PANSS reflects more severe symptoms. The PANSS test has been shown to be correlated with criterion measures, with an inter-rater reliability about 0.80 [36]. The Cronbach's alpha of Iranian version has been 0.73 to 0.83 [37].

The evaluation was performed at zero, second and fourth weeks. All questionnaires were fulfilled by a certain person, to avoid any bias. As the study was double-blind, neither the patient, nor the evaluator, were aware that the patient is receiving true medicine or placebo. Finally, data were analyzed

by using the SPSS software version 13, using chi-square and Fisher's exact tests for the assessment of homogeneity of 2 groups, paired t test for evaluation of improvement in each group during the experiment and independent t test for the comparison of the improvement rate of 2 groups.

### 2.5. Statistical Power

It should be noted that when calculating the sample size in the present study, a similar study on the combination of clozapine and celecoxib was not found for calculating the sample size according to its results, thus at first pilot study on 20 patients (10 in each group, participants who were randomly selected from eligible patients) was performed. Based on the results, the sample size in each group calculated 16, considering  $\alpha = 0.05$  and  $\beta = 0.2$ , but according to 15% drop out in the pilot study, to reach the minimum in each group, 40 eligible patients were randomly assigned to two groups of 20. Finally, a group of 17 control patient and the other 18 patients were studied.

### 3. Results

In this study, 40 patients with schizophrenia participated and

were randomly divided into 2 equal groups. The experimental group received clozapine and celecoxib, while the control group received clozapine and placebo. No adverse drug side effects was seen in patients during the experiment. As 5 non-cooperative patients left the study, it continued with 35 patients (17 and 18 patients in experimental and control groups, respectively).

The experimental group consisted of 15 men and 2 women, while the control group included 15 men and 3 women. Fisher's exact test showed that there was not a significant gender difference between 2 groups ( $P=0.582$ ). Mean age in experimental and control groups was  $29.4 \pm 14.3$  and  $27.8 \pm 14.2$  years, respectively and independent t test showed that they were not significantly different ( $P=0.480$ ). Mean dosage of clozapine in experimental and control groups was  $88.29 \pm 15.86$  and  $87.28 \pm 14.97$  mg/day, respectively and independent t-test showed that it was not significantly different ( $t=0.949$ ,  $P=0.350$ ). Also, chi-square test showed that frequency of hospitalization was similar in 2 groups ( $X^2=1.7$ ,  $df=3$ ,  $P=0.633$ ). The demographic information of the study groups have been indicated in table 1.

**Table 1.** The demographic data of the study participants based on group

Variables	Groups	Frequency	Percent	X2	P	
Gender	Experimental	Female	2	11.76	0.874	0.582
		Male	15	88.23		
	Control	Female	3	16.66		
		Male	15	83.33		
Frequency of hospitalization	Experimental	0	7	41.2	1.7	0.633
		1	3	17.6		
		2	2	11.8		
		>2	5	29.4		
		Total	17	100		
	Control	0	6	33.3		
		1	5	27.8		
		2	4	22.2		
		>2	3	16.7		
	Total	0	13	37.1		
		1	8	22.9		
		2	6	17.1		
>2		8	22.9			
Total		35	100			
Age(years)	Mean $\pm$ SD				0.480	
	Experimental		$29.4 \pm 14.3$			
	Control		$27.8 \pm 14.2$			

**Table 2.** Paired t test for comparison of positive and negative syndrome scale (PANSS) sub-scales between 0, 2nd and 4th weeks in each of experimental and control groups (Both groups had a significant improvement of all PANSS sub-scales in 2nd and 4th weeks)

Positive and Negative Syndrome Scale (PANSS) Sub-scales	Group	0 week		2nd week		4th week		Comparison between 0 and 2nd weeks		Comparison between 2nd and 4th weeks	
		Mean	SD	Mean	SD	Mean	SD	t	P	t	P
Positive symptoms	Experimental	29.94	4.88	26.35	4.04	23.88	3.44	8.450	<0.001	8.154	<0.001
	control	29.83	4.88	26.72	3.51	24.66	3.62	8.390	<0.001	8.132	<0.001
Negative symptoms	Experimental	30.24	4.53	26.52	4.19	23.05	3.76	8.374	<0.001	8.265	<0.001
	control	30.11	3.85	26.77	3.7	23.94	3.66	8.354	<0.001	8.305	<0.001
General psycho-pathology	Experimental	47.94	8.12	43.82	7.78	41.58	7.41	7.879	<0.001	7.359	<0.001
	control	47.82	85.4	44	8.02	42.5	7.74	7.536	<0.001	7.383	<0.001
Total score	Experimental	108.12	16.30	96.7	14.85	88.52	13.43	8.235	<0.001	8.149	<0.001
	control	107.83	15.56	97.5	13.56	90.66	12.88	8.192	<0.001	8.180	<0.001

**Table 3.** Independent t test for comparison of positive and negative syndrome scale scores between experimental and control groups: Difference between two groups isn't significant

Positive and Negative Syndrome Scale (PANSS) Subscales	Time	Group	Mean	SD	df	t	P
Positive symptoms	0 week	Experimental	29.94	4.88	33	0.1	0.984
		control	29.83	4.88			
	2nd week	Experimental	26.35	4.05	33	0.3	0.774
		control	26.72	3.51			
	4th week	Experimental	23.88	3.44	33	0.7	0.517
		control	24.67	3.63			
Negative symptoms	0 week	Experimental	30.24	4.53	33	0.1	0.931
		control	30.11	3.85			
	2nd week	Experimental	26.53	4.2	33	0.2	0.854
		control	26.78	3.7			
	4th week	Experimental	23.06	3.77	33	0.7	0.486
		control	23.94	3.67			
General psychopathology	0 week	Experimental	47.94	8.12	33	0.1	0.985
		control	47.82	85.4			
	2nd week	Experimental	43.82	7.79	33	0.1	0.948
		control	44.00	8.02			
	4th week	Experimental	41.59	7.42	33	0.2	0.857
		control	42.06	7.75			
Total score	0 week	Experimental	108.12	16.30	33	0.1	0.958
		control	107.83	15.56			
	2nd week	Experimental	96.71	14.86	33	0.2	0.870
		control	97.50	13.57			
	4th week	Experimental	88.53	13.43	33	0.5	0.634
		control	90.67	12.88			

Experimental and control groups had similar PANSS scores (regarding positive symptoms, negative symptoms, general psychopathology and total score) at the baseline ( $P > 0.05$ ). Paired t test showed that both experimental ( $P < 0.001$ ) and control ( $P < 0.001$ ) groups experienced a significant improvement of all sub-scales of PANSS in both second and fourth weeks. Improvement of PANSS scores during the experiment in experimental group was a little better than the control group, however, independent t test showed that it was not significant ( $P > 0.05$ ) (tables 2 & 3).

#### 4. Discussion

Although both groups experienced significant improvement in all PANSS domains in second and fourth weeks ( $P < 0.001$ ), the difference between the two groups were not significant ( $P > 0.05$ ). This finding did not support results of prior studies that report a significant effect for celecoxib as an add-on to atypical antipsychotics.

The considerable improvement is observed in the second week of treatment and remains significant even until the fourth week. However, 200 mg/day of celecoxib is not prior than placebo to provide a significant improvement.

Studies suggest that inflammatory system activities can deteriorate some functions in schizophrenia such as cognitive affective, emotional and social functions. It means inflammatory system has a role in the development of schizophrenia especially in negative and cognitive symptoms [19].

For the first time in 2002, Muller and colleagues showed that 5 weeks of treatment with risperidone (2-6 mg/day) plus celecoxib (400 mg/day) improves positive, negative and total symptoms of schizophrenia better than risperidone alone [14]. This provoked a number of studies about the role of

COX-2 inhibitors in the treatment of schizophrenia. The priority of 8 weeks of treatment with risperidone (6 mg/day) plus celecoxib (400 mg/day) compared to risperidone alone for the improvement of positive symptoms, general psychopathology and PANSS total score was emphasized by Akhondzadeh et al. Though, the rate of extrapyramidal side effects was not significantly affected [22]. A study on patients with the first manifestation of schizophrenia demonstrated that 400 mg/day of celecoxib plus 200-1000 mg/day of amisulpride, affects the negative symptoms, as well as the general psychopathology and PANSS total score [27]. Also, in another study it was detected that celecoxib ameliorates the cognition of patients with schizophrenia [38].

These findings support the hypothesis that an immunological dysfunction exists in the pathogenesis of schizophrenia and COX-2 enzyme is involved here. However, in a study celecoxib was not capable of altering the cytokine levels in patients with schizophrenia receiving stable doses of olanzapine or risperidone [39].

Although most of the studies concerning the benefits of COX-2 inhibitors were promising, Rapaport et al did not find any advantage in using 400 mg/day of celecoxib for 8 weeks compared to placebo, in treatment of continuously ill schizophrenic outpatients receiving a stable dose of an atypical antipsychotic [24]. In a cohort, Stolk et al showed that exposure to COX-2 inhibitors in patients with schizophrenia using antipsychotics may not decrease the risk of deterioration [25].

A number of probable reasons are suggested for these inconsistent results concerning the effect of celecoxib in schizophrenia. Muller prescribed 400 mg/day of Celebrex [14], while in the present study our patients received low dosages



of celecoxib (200 mg/day) of an Iranian drug corporation. This difference of dosage and efficacy could affect the therapeutic results with a high probability.

Evidence shows that clozapine can be effective on patients with schizophrenia who are resistant to other antipsychotics [27]. This high efficacy of clozapine may have reached our patients to maximum of therapeutic outcomes and prevented the probable therapeutic effects of celecoxib to appear.

Drug interactions may also impress the results in several ways. For instance, if celecoxib has the ability to induce the metabolism of clozapine, as the metabolites of clozapine have very little antipsychotic effects compared to metabolites of risperidone [27], it will reduce the efficiency of combination of clozapine and celecoxib, compared to risperidone and celecoxib. On the other hand, the COX-2 enzyme interacts with both serotonergic and cholinergic receptors [12]. Clozapine and risperidone, both affect these receptors, but in different ways [27, 30]. So, it would not be amazing if clozapine and risperidone had different interactions with COX-2 inhibitors, resulting in inconsistent results.

It is notable that most studies have focused on other atypical antipsychotics, except clozapine. A recent study indicates anti-inflammatory effects of some atypical antipsychotics via inhibition of activated microglia. Maybe clozapine works in different ways [40]. Extended studies are needed to clarify this.

Nutrition and habitual behaviors may also interact. For instance, smoking cigarette decreases the effect of several antipsychotic, through an unknown way [41]. Also, excessive consumption of vitamin C reduces the effect of fluphenazine [42]. Laboratory research suggests that xanthine of tea and coffee interacts with the effects of neuroleptics [43], however a study on human beings did not confirm that effect [44].

Finally, as it was said, increases of the CSF level of IL-2 results in the appearance of the treatment resistant cases of schizophrenia [7]. It is said that clozapine is effective on resistant cases [27]. So, clozapine may have some immunologic effects and functions through reducing the CSF level of IL-2. These probable immunologic effects must be regarded too.

In some cases, patients who had improvement, persisted to release before completing the experiment and this made some disturbances. Also, it was appropriate to evaluate plasma levels of consumed drugs and their metabolites to declare if there is an interaction between them or not, but it did not become available at the moment.

Although this study did not confirm that 200 mg/day of celecoxib, as an add-on to clozapine, has a significant additional effect on schizophrenia symptoms comparing with clozapine alone, the selection of a low dosage and some probable interfering factors, suggest that more precise, extensive and controlled studies are required in this field. There are only few studies about the relationship between the unique adverse and therapeutic effects of clozapine. Approximately

half of the patients develop fever and flu like syndrome during the first month of clozapine administration. Furthermore, the risk of side-effects increases within the same time. Both of these events, may be related to increasing cytokines and immunological system activities [28], so co administration of clozapine and low doses of celecoxib may prevent some adverse effects of clozapine without decreasing the therapeutic effects of clozapine. Further investigations in this field are suggested to clarify this.

As peripheral and central inflammatory responses of schizophrenic patients are activated and have a role in negative and cognitive symptoms of schizophrenia [19], augmentation of anti-inflammatory drugs such as celecoxib may be useful. Additional benefits can be due to reducing some comorbid somatic diseases and mortality rate of cancer in these patients [45]. However, further research is deserved.

## 5. Conclusion

Regarding the safety of the combination of celecoxib and clozapine that was observed in patients with schizophrenia, it will be appropriate for the next studies to use high dosages of celecoxib, which may be more efficient. Following patients for more weeks, may appear some long term therapeutic effects of clozapine and celecoxib co-administration. In less acute cases, it is better to evaluate the antipsychotic effects of celecoxib, as a mono-therapy, to avoid drug interactions. Otherwise it is suitable to measure the plasma levels of drugs in order to interpret more precisely. Environmental factors, such as nutrition and smoking should be controlled too. It will be appropriate to assess the plasma and CSF levels of inflammatory cytokines simultaneously. Studying genes responsible for the appearance of different efficiency of antipsychotics in different people would be beneficial too. As some COX-2 inhibitors such as rofecoxib have been shown promising in other psychiatric disorders, such as depression, they require appropriate clinical trials to be done [12]. Conducting clinical trials concerning the benefits of other neuroprotective agents, such as memantine are useful as well [46]. The next studies will be hopeful to provide more efficient treatments for schizophrenia, in order to approach its definite cure.

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## Authors' Contributions

Ali Akhoundpour Manteghi: Data collection, study design, contribution to the manuscript. Roya Samadi: Literature search, concept and design of the study, editing and review of the manuscript. Mehri Baghban Haghighi: Statistical analysis, literature search of manuscript, manuscript preparation. Amin Azhari: Data collection, study design, literature

search of manuscript. Shervin Assari: Study design, and contribution to the manuscript draft and revision.

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