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The Differences in Adjuvant Therapy Effectiveness Meloxicam and N-Acetylcysteine against Negative Symptoms of Schizophrenia

Banu Kadgada Kalinga Murda[1], I Gusti Indro Nugroho[2*], Adriesti Herdaetha[3]

[1]Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.
[2]Department of Psychiatry, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.
[3]Dr. Arif Zainuddin Regional Mental Hospital Surakarta/Universitas Sebelas Maret, Surakarta, Indonesia.

A B S T R A C T

Introduction: Meloxicam and N-Acetylcysteine are examples of drugs with anti-inflammatory effects that have been widely studied, and are considered to reduce negative symptoms of schizophrenia. Both of these drugs are also widely available in Indonesia and can be obtained at an affordable price. This study aimed to analyze the differences in the effectiveness of adjuvant therapy meloxicam and N-Acetylcysteine on negative symptoms of schizophrenic patients.

Methods: This was a quasi-experimental study using a single-blind, pretest–post-test design. Determination of the subject used a purposive sampling technique according to the inclusion criteria. This study examined 34 samples and divided them into two groups. In group A, 17 subjects received adjuvant meloxicam therapy of 15 mg/day for 4 weeks; in group B, 17 subjects received adjuvant therapy of N-Acetylcysteine 400 mg/day for 4 weeks. Score assessment was performed using the positive scale, negative scale, and general psychopathology scale (PANSS) negative subscale pre- and post-therapy, then compared the effectiveness. Data analysis used SPSS 25.0.

Results: The mean score of the PANSS post-test subscale was negative in the meloxicam adjuvant therapy group 15.58, while for the N-Acetylcysteine adjuvant therapy group was 17.64 with a p-value of 0.009. The mean decrease in the negative subscale PANSS score in the meloxicam adjuvant therapy group was 11.00, while the N-Acetylcysteine adjuvant therapy group was 19.70 with a p-value of 0.000.

Conclusion: There was no difference in the effectiveness of adjuvant therapy meloxicam and N-Acetylcysteine in improving negative symptoms of schizophrenic patients.

Highlights:

1. Schizophrenic patients can have negative symptoms.
2. Adjuvant therapy is needed to assist antipsychotics in reducing the negative symptoms of schizophrenic patients.

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* Correspondence: indronugrohopsy@gmail.com

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Introduction

A chronic disease that can cause disability in about 1% of the world's human population is called schizophrenia. Schizophrenia also has the trait of passing on to the next generation, estimated at 80%. The onset of this disease generally occurs in late adolescence or early adulthood.[1] The prevalence of schizophrenia in Indonesia reaches 0.3–1%. Based on data from medical records at Dr. Arif Zainuddin Regional Mental Hospital (RSJD), Surakarta 2019, 21,008 schizophrenic patients visited, of which 18,861 were outpatients, and 2,147 were inpatients.[2]

Schizophrenia consists of negative, positive, and cognitive symptoms. Negative symptoms could significantly impact the patient, such as performing activities of daily living, the patient's ability to live independently, be socially active, work or study, and maintain personal relationships. This will certainly disrupt the lives of patients and their families in the future. Schizophrenia causes great losses in social life and in terms of lost productivity and large medical expenses. In addition, the presence of persistent negative symptoms is a predictor of a worse patient prognosis compared to positive symptoms.[3]

Non-pharmacological therapies such as cognitive behavioral therapy (CBT) and motivation and engagement training (MOVE) could optimize the treatment efficacy.[4] Other therapy such as cognitive enhancement therapy (CET) could improve the quality of life for patients with schizophrenia.[5] Family models could also be applied in schizophrenia management. The concept aids families in managing their stress by reducing burden and stigma. Hence, the patients can survive, rise, become stronger, and provide better care for schizophrenic patients.[6] There needs to be a long-term cure for schizophrenia. High treatment adherence may reduce the symptoms of schizophrenia and guard against relapse. Family support is essential to ensure that the patients continue to take their medication regularly.[7]

“Adverse symptoms” is a general definition regardless of the cause, long-term stability, or the symptoms' duration. Meanwhile, some negative symptoms are signs that may be observed by clinicians (e.g. flattened emotions, alogies), and other behavioural factors, such as decreased engagement in productive or enjoyable activities and social withdrawal. Therefore, inquiring about patients’ concerns, motivations, and emotions is of great value in observing patients while evaluating negative symptoms. Although various specific words are used to decipher the etiology of negative symptoms (e.g., predominance, deficit, persistence), the term is no agreed definition.[8]

Several pharmacological and other treatments have been introduced that go beyond conventional treatments. Nevertheless, many things remain unresolved. While running with the terrible signs of schizophrenia, it was diagnosed early that they might originate secondary to many conditions. These blanketed long-time period institutionalization, loss of environmental stimuli, terrible value improved significantly.[15,16] Seeing the good results of the adjuvant administration of meloxicam and N-social support, secondary to fine signs, different psychiatric ailments such as depression, and exacerbations of the disorder as such or even antipsychotic medications.[9]

Distinguishing between primary and secondary negative symptoms is important for researchers and clinical trial design, but these symptoms can be difficult to distinguish. Therefore, the clinical focus should be on managing negative symptoms that affect patients who do not respond to current therapy, persist during the clinical stability period, and interfere with normal role functioning. Physicians should ensure that patients with only clinically significant negative symptoms (i.e., predominant negative symptoms) or positive symptoms (i.e., prominent positive symptoms) benefit from appropriate clinical management.[8] However, there are currently no approved treatments for serious illness in the United States. Persistent negative symptoms (PNS) that do not respond to treatment for secondary causes. Pharmacologic and psychosocial treatments are currently available, developed, and tested with heavy and PNS as primary targets. Academicians, clinicians, the pharmaceutical industry, research funders, payers, regulators, and researchers should collaborate to develop new treatments to address this major public health problem.[10]

Recently, new antipsychotics have been discovered, and the negative symptoms of schizophrenia are not even responding to these pharmacotherapies. The high level of social disorders and chronic worsening of the symptoms suffered indicate that schizophrenia has neurodegenerative characteristics.[11] Although the exact cause of schizophrenia is still unknown, many researchers suggest that the immune system may be involved in the pathogenesis of schizophrenia.[12] Along with genetic and neurodegenerative factors, inflammation has also been considered a major causative and/or mediating factor in schizophrenia.[11] Inflammatory markers such as proinflammatory cytokines are etiologic factors found in psychiatric disorders, including schizophrenia. One mechanism involves chronic activation of macrophages, T lymphocytes, and microglia that secrete proinflammatory cytokines such as Interleukin-4 (IL-4), Interleukin-2 (IL-2), Interleukin-10 (IL-10), Interleukin-6 (IL-6), and Interferon Gamma (IFN-γ).[13]

As a result of the absence of antipsychotics that can improve negative symptoms and the strong suspicion of the participation of proinflammatory cytokines in the process of schizophrenia, adjuvant therapy with an effective and efficient anti-inflammatory effect is needed. A meta-analysis that evaluated the efficacy and tolerability of non-steroidal anti-inflammatory drugs (NSAIDs) as adjuvant therapy in treating schizophrenia showed that NSAID adjuvant therapy outperformed placebo with respect to the improvement of negative symptoms.[14] A randomized double-blind controlled trial assessing the effect of N-Acetylcysteine showed that N-Acetylcysteine could significantly improve negative symptoms. The meta-analysis conducted by Yolland, *et al*. (2020) and Cho, *et al*. (2019) showed that the total PANSS and negative subscale Acetylcysteine against the negative symptoms of schizophrenia and the easy availability of these drugs in

Indonesia at a relatively affordable price, this study wanted to see differences in the effectiveness of giving meloxicam and N-acetylcysteine to improve negative symptoms in schizophrenic patients in Indonesia.

This study aimed to analyze the differences in the effectiveness of meloxicam and N-Acetylcysteine as adjuvant therapy in reducing negative symptoms in schizophrenic patients.

Methods

This study used a quasi-experimental research design, single-blind, pretest–post-test design performed at the Inpatient Unit of RSJD from May to July 2020. The samples were schizophrenic patients who were given antipsychotic combination therapy (risperidone–chlorpromazine, and/or haloperidol injection) and were hospitalized at RSJD who met the inclusion and exclusion criteria from May to July 2020. The research sample was taken by purposive sampling.

Inclusion Criteria

Schizophrenic patients who were hospitalized at RSJD from May to July 2020 were treated with a combination of antipsychotic risperidone–chlorpromazine, and/or haloperidol injection, aged 18-40 years old, and got the approval from the caregiver.

Exclusion Criteria

Schizophrenic patients with organic disorders (such as epilepsy, stroke, and mental retardation or head injuries with a history of decreased consciousness), substance and alcohol abuse, taken anti-inflammatory drugs or steroids or taken anti-inflammatory drugs or steroids for less than one month, and got electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS).

In a quasi-experimental study, the sample size of each treatment group should be in the range of 15 to 20 samples.[17] Calculation of research subjects is determined by using a formula.

(t-1) (n-1) 15
(2-1) (n-1) 15
(n-1) 15
n 15 = 15+10% = 15+1.5 = 15+2
n 17

t: number of treatment groups
n: number of research subjects per treatment group

Thus, the minimum number of samples for each group in this study was 17 subjects. The data obtained were tabulated and analyzed to determine the difference in the effectiveness of adjuvant therapy between meloxicam and N-Acetylcysteine in reducing negative symptoms, with unpaired T-group analysis if the data distribution was normal, and the Mann-Whitney test if the data distribution was not normal. The difference was significant when the resulting p-value < 0.05. All statistical analyzes used SPSS 25.0.

The sample size in this study was 34 subjects who had met the inclusion and exclusion criteria. All samples were divided into two groups, namely group A with 17 research subjects and group B with 17 research subjects. Subjects in group A received adjuvant meloxicam 15 mg per day (morning) for 4 weeks, in addition to combination antipsychotic therapy of risperidone–chlorpromazine, and/or haloperidol injection, while subjects in group B received adjuvant N-acetylcysteine 400 mg per day (morning and night) for 4 weeks, in addition to risperidone–chlorpromazine combination antipsychotic therapy, and/or haloperidol injection.

The research subject data was obtained from the negative subscale PANSS score assessment results. After all research data had been collected, data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 25.0 program. From the study, data were obtained about the demographic characteristics of the research subjects and the results of differences in the effectiveness of meloxicam and N-Acetylcysteine against negative symptoms. The data obtained are presented in tabular form.

Results

Based on Table 1, the two groups performed a comparative test with the Mann-Whitney test for age and negative subscale PANSS pre-test scores, Fisher's Exact test for gender, and Chi-Square for education. The results obtained statistically showed that there was no significant difference between the meloxicam adjuvant group and the N-Acetylcysteine adjuvant group in the type gender (p = 0.225) because the p-value> 0.05. For the meloxicam adjuvant group and the N-Acetylcysteine adjuvant group in age (p = 0.021), education (p = 0.000), and PANSS pre-test score negative subscale (p = 0.000), there was a significant difference because the p-value < 0.05.

Table 2 describes the results of the pre-test, post-test, and a decrease in the negative subscale PANSS score in the adjuvant meloxicam and N-Acetylcysteine. The data had been tested for normality and homogeneity. The data obtained were not normally distributed. From the results of statistical calculations, the average results in the meloxicam adjuvant group showed a mean score of PANSS negative subscale pre-test of 26.58 ± 4.57 (95% CI: 24.23 - 28.93), the mean score of PANSS subscale negative post-test was 15.58 ± 2.42 (95% CI: 14.34 - 16.83), and the mean decrease in the negative subscale PANSS score was 11.00 ± 4.40 (95% CI: 8.73 - 13.26). In addition, the results for the adjuvant group were also obtained N-Acetylcysteine with the mean of pre-test negative subscale PANSS score was 37.35 ± (95% CI: 34.53 - 40.16), the mean of post-test negative subscale PANSS score mean was 17.64 ± 0.70 (95% CI: 17.28 - 18.00), and the mean decrease in the negative subscale PANSS score was 19.70 ± 5.49 (95% CI: 16.87 - 22.53)

Table 1. Demographic characteristics of research subjects

Characteristics	Group		p-value
	Meloxicam	N-Acetylcysteine	
Age			
Mean ± SD	34.76 ± 5.14	31.47 ± 4.85	0.021*
Gender			
Man	11 (32.4%)	15 (44.1%)	0.225**
Woman	6 (17.6%)	2 (5.9%)	
Education			
< Middle school	14 (41.2%)	1 (2.9%)	0.000***
≥ Middle school	3 (8.8%)	16 (47.1 %)	
PANSS pre-test score subscale negative			
Mean ± SD	26.58 ± 4.57	37.35 ± 5.48	0.000*

*Mann-Whitney test; **Fisher's Exact test; ***Chi-Square test

Statistical calculations showed significant results on the mean pre-test, post-test, and negative subscale PANSS scores in the adjuvant meloxicam and N-Acetylcysteine with p-value < 0.05. From the data obtained, it can be described that the subjects in the N-Acetylcysteine group had more severe negative symptoms compared to the Meloxicam group. The meloxicam group and the N-Acetylcysteine group had unequal baseline data. This can be seen from the results of statistical calculations, which showed a significant difference in the mean score of the initial negative PANSS subscale in the two groups. Hence, it can be said that the sample of this study was not normally distributed.

This study found that the meloxicam adjuvant group and the N-Acetylcysteine group experienced a decrease in the negative subscale PANSS score in both groups. There was also a difference in the mean difference in the decrease in the negative subscale PANSS scores. In the N-Acetylcysteine adjuvant group, the mean decrease in the negative subscale PANSS score was greater than in the meloxicam adjuvant group. After analyzing with statistical calculations, there was a significant difference in the mean decrease in the negative subscale PANSS score. However, it should also be noted that the mean post-test negative subscale PANSS score in the meloxicam adjuvant group was better than the N-acetylcysteine adjuvant group. Thus, it can be said that adjuvant therapy with meloxicam 15 mg/day and N-Acetylcysteine 400 mg/day was equally effective in improving negative symptoms in schizophrenic patients who were hospitalized at RSJD.

These results are in accordance with the study conducted by Cho, *et al*. (2019) who conducted a meta-analytic investigation of randomized controlled trials (RCT) which stated that adjuvant therapy with NSAIDs and N-Acetylcysteine could significantly improve the total negative subscale PANSS score in schizophrenic patients.[16] Purwono (2018) also conducted a study with the conclusion that adjuvant meloxicam therapy effectively reduced Hs-CRP levels and improved PANSS scores.[18] A study conducted by Sepehrmanesh, *et al*. (2018) also showed that adjuvant N-Acetylcysteine therapy with conventional antipsychotic drugs in 84 chronic schizophrenic patients showed a significant improvement in negative symptoms.[19] N-Acetylcysteine was also well tolerated.

Discussion

Cho, *et al*. (2019) also reviewed the extrapyramidal symptoms rating scale (ESRS) and abnormal involuntary movement scale (AIMS) scores on NSAIDs and N-Acetylcysteine.[16] This study showed that there were no significant side effects of NSAID and N-Acetylcysteine adjuvant therapy in schizophrenic patients. In this study, no side effects were found in the study subjects during adjuvant therapy with meloxicam and N-Acetylcysteine. Another mental illness that could be measured using a scale is anxiety through the Hamilton Rating Scale for Anxiety which elaborated on medical students and shows fifth-year medical students had the highest frequency of anxiety.[20]

Meloxicam is a COX-1/2 inhibitor, which has stronger COX-2 inhibitory properties than COX-1 inhibition. COX-2 inhibitors are selective for COX-2 and help reduce pain and inflammation by reducing the risk of damage to the stomach lining and do not affect platelet function.[21] As NSAID drugs, Meloxicam is used to treat arthritis. Additionally, to be effective in treating arthritis, COX-2 inhibitors have been revealed to potentially delay the onset of Alzheimer's disease via reducing inflammation in the early stages of Alzheimer's disease.[22,23] COX-2 is the most abundant isoenzyme in the brain area which is implicated in psychiatric disorders. COX-2 enzymes are known to interact with neurotransmitters, such as serotonin, glutamate, and acetylcholine. Additionally, as an inflammation regulator in the central nervous system (CNS) by acting on prostaglandins.[24,25]

In oral use, the pharmacokinetic dose proportional to meloxicam capsules is in the range of 7.5–15 mg. Maximum levels are reached 4-5 hours after taking meloxicam. Concentration steady state achieved on the fifth day.[26] The absorption of meloxicam is relatively slow, has a half-life of up to 20 hours, and is converted to inactive metabolites. The use of meloxicam 7.5-15 mg/day has a lower ulcerogenic side effect compared to the use of other NSAIDs.[27] N-Acetylcysteine shown to act on several pathways involved in various psychiatric disorders are oxidative stress, inflammatory mediators, nerve transmission, and neural plasticity.[28] N-Acetylcysteine is a glutathione (GSH) precursor, an intracellular antioxidant that neutralizes reactive oxygen and nitrogen through direct and indirect mechanisms.[29] It can cross the blood-brain barrier (BBB) unlike oral glutathione.[30] It has anti-inflammatory properties through several cellular processes. GSH precursors and antioxidants directly inhibit upstream events leading to the activation of Nuclear Factor-κβ (NF-) and other proinflammatory cytokines. The inhibition of the proinflammatory transcription factor NF- by N-Acetylcysteine down-regulates the expression of several proinflammatory genes.[31]

A study proved that N-Acetylcysteine therapy could improve negative, positive, general, and global psychopathological symptoms. N-Acetylcysteine was also

safe, easy to use, and well-tolerated in schizophrenic patients.[19] Oral N-Acetylcysteine is well-tolerated and gives no significant side effects, proven by clinical trials for psychiatric disorders, with the recommended dose of 2000-2400 mg per day.[32] A previous study about N-Acetylcysteine revealed that the effects of N-Acetylcysteine on symptoms may be related to structural integrity, but N-Acetylcysteine fails to show therapeutic effects on longitudinal measures of brain morphology was.[33]

N-Acetylcysteine has been proposed in many diseases, including as an anti-suicide. Suicidal thoughts were more prevalent in those who were younger in age, had illnesses that lasted longer, scored lower on the Global Assessment of Functioning (GAF) scale, were largely female, were unemployed, made less money, and had less education.[34] N-Acetylcysteine might be involved in glutamate metabolism resulting as a rapid antidepressant effect.[35] The interventions of N-Acetylcysteine have been investigated, and it consistently reported the effects on negative symptoms, whereas cognitive and positive symptoms are still questioned.[36] However, the duration of N-Acetylcysteine treatment should be longer for the success of the treatment.[15] N-Acetylcysteine has involvement in neurobiological effects such as inflammation, the signaling of glutamate, the regeneration of mitochondrial energy and apoptosis, and the other pathways that dysregulate schizophrenia.[37,38] N-Acetylcysteine has beneficial effects as an adjunctive agent in schizophrenia negative symptoms, including depression, severe autism, obsessive-compulsive disorder, and other related disorders.[39]

Table 2. Changes in the negative subscale PANSS score after the intervention

Parameter	Mean	SD	Min – Max	95% CI	p
PANSS pre-test					
Meloxicam	26.58	4.57	21 – 37	24.23 – 28.93	0.000
N-Acetylcysteine	37.35	5.48	27 – 45	34.53 – 40.16	
PANSS post-test					
Meloxicam	15.58	2.42	12 – 19	14.34 – 16.83	0.009
N-Acetylcysteine	17.64	0.70	16 – 19	17.28 – 18.00	
PANSS drop					
Meloxicam	11.00	4.40	5 – 21	8.73 – 13.26	0.000
N-Acetylcysteine	19.70	5.49	9 – 27	16.87 – 22.53	

Source: Research data, processed

Neuropsychiatric disorders such as bipolar disorder, depression, and schizophrenia are common. It shows the course of neuro-progression from the prodromal stage to chronicity. There are many drugs with the ability to attenuate the biological mechanisms associated with neuro-progression. Signs of clinical neuroprotection are evident for many drug candidates. The combination of multiple agents may represent a viable avenue for the clinical realization of neuroprotection. Definitive prospective studies on neuroprotection using multimodal assessment tools are needed.[38]

Several risk factors for developing psychosis disorders such as schizophrenia have been revealed, such as the genetic contribution of identical twins having a 46% possibility of developing schizophrenia. Environmental exposures also supported the development of schizophrenia, such as birth complications, malnutrition, infectious diseases, birth season, and history of substance abuse.[40,41] The adjuvant administration of meloxicam 15 mg/day and N-Acetylcysteine 400 mg/day for 4 weeks are expected to provide effective and efficient therapeutic results. This study collaborated with the doctor in charge of the PANSS assessment and the room nurse supervising the administration of additional therapy and side effects.

Strength and Limitations

The strength of this study was that the sample selection was performed randomly, and interrater assessors performed the PANSS assessment. The limitation of this study was that the length of history of schizophrenia was not included. Hence, it is not known about the effectiveness of the adjuvant meloxicam and N-acetylcysteine on the degree or severity of schizophrenia.

Conclusion

PANSS subscale scores in the meloxicam adjuvant group were better than the N-Acetylcysteine adjuvant group, but the N-Acetylcysteine adjuvant group showed a greater mean decrease in the negative subscale PANSS scores. There was no difference in the effectiveness of adjuvant therapy meloxicam and N-Acetylcysteine in improving negative symptoms of schizophrenic patients hospitalized at RSJD Surakarta.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Ethics Committee for Health Research, Dr. Moewardi General Academic Hospital, Surakarta (no. 1.410/XI/HERC/2020) on 8 April 2020.

Authors' Contributions

Designing and implementing the research, analyzing the results, writing of the manuscript: BKKM, IGIN, AH

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