Open Access Maced J Med Sci **electronic publication ahead of print,**
published on May 31, 2019 as https://doi.org/10.3889/oamjms.2019.461

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.461
eISSN: 1857-9655
Clinical Science

The Indonesian Version of Montreal Cognitive Assessment (MoCA-Ina): The Difference Scores Between Male Schizophrenia Prescribed by Risperidone and Adjunctive of Donepezil in Public Hospital of Dr Pirngadi Medan, Indonesia

Novita Linda Akbar*, Elmeida Effendy, Vita Camellia

Department of Psychiatry, Universitas Sumatera Utara, Medan, Indonesia

Citation: Akbar NL, Effendy E, Camellia V. The Indonesian Version of Montreal Cognitive Assessment (MoCA-Ina): The Difference Scores Between Male Schizophrenia Prescribed by Risperidone and Adjunctive of Donepezil in Public Hospital of Dr Pirngadi Medan, Indonesia. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.461

Keywords: Schizophrenia; Donepezil; Cognitive functions; MoCA-Ina

***Correspondence:** Novita Linda Akbar. Department of Psychiatry, Universitas Sumatera Utara, Medan, Indonesia. E-mail: novitalindaakbar@gmail.com

Received: 27-Mar-2019; **Revised:** 20-May-2019; **Accepted:** 21-May-2019; **Online first:** 31-May-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Prescribing donepezil as an addition in reducing the cognitive dysfunctions among schizophrenia patients that have been given by antipsychotic (risperidone and olanzapine) is commonly used. Also, to determine the presence of the dysfunctions, an assessment is conducted by Montreal Cognitive Assessments based on Indonesian version (MoCA-Ina) to provide a more understandable test.

AIM: To determine the score differences of MoCA-Ina between male patients of schizophrenia prescribed with only risperidone, and those with the addition of Donepezil within a certain interval of times.

SETTINGS AND DESIGN: It is a pre-post-test experimental design with non-probability of consecutive sampling.

METHODS: The study involved 48 of schizophrenia patients who have been prescribed fixed dose risperidone for 4 mg/day orally, and 24 people who were the intervention group were prescribed with the additional of 5 mg of donepezil per day started from the first until sixth week, followed by the increased dosages to 10 mg until twelfth week. These patients were recruited from the Public Hospital of Dr Pirngadi Medan, Indonesia, under the Department of Psychiatry. Then, the statistical data were analysed by Mann Whitney U, Friedman, and Wilcoxon, followed by analysing of SPSS version 21.

RESULTS: The addition of five mg of Donepezil increased the MoCA-Ina score significantly compared to those who only prescribed with risperidone during all weeks of observation.

CONCLUSION: Based on the results, the addition of donepezil increased the score level of the MoCA-Ina in the intervention group.

Introduction

Schizophrenia is one of the most confusing brain impairment, which is indicated by the manifestation of acute psychotic followed by continuous dysfunction of cognitive and antisocial personalities [1]. There are many different targets and strategies that have been used to improve the cognitive functions to schizophrenia patient; however, the therapeutic therapies relatively have found the difficulties [2]. Therefore, seven cognitive domains have been identified to be considered as molecular targets in treating the schizophrenia patients cognitively, including working memory, attention and vigilance, speed of processing, verbal and memory learning, visual and memory learning, reasoning and problem solving, and social cognition [3]. In current medical developments, schizophrenia is present due to the mental disturbance of simulations, indicated by several emotional disruptions, ideational, and cognitive dysfunctions. Regarding cognitive disturbances, the dysfunction parameters are observed in term of active and controllable processing information, such as the speed of thinking, attention, and awareness, and this happens because of the alteration within the neurochemical and neuropathological factors. Several studies have reported that the cholinergic neurotransmitter system involving the nicotinic and muscarinic receptors is

important to stimulate the neuromodulator of the cognition process to schizophrenia, despite dopamine as the main reason [4].

In addition, to improving the cognitive functions among schizophrenia patients, several antipsychotic medications are used, such as olanzapine, and risperidone, as temporal considerations. A study has reported that the second generation of antipsychotic medications, such as donepezil can stimulate the prefrontal cortex so that the cognitive functions could be improved [1]. This medication is one of the acetylcholinesterase inhibitors, which is a reversible inhibitor from the asetlkolinesterase enzyme, known chemically as *(±) - 2, 3 -dihydro-5, 6 - dimethoxy – 2 - [[1- (phenylmethyl) - piperidinyl] - 1H – in - 1-one hydrochloride*. The donepezil hydrochlorides are known as E2020 in pharmacology literature [4], consumed to obtain the therapeutic effects to increase the cholinergic functions. This is consumed by increasing the acetylcholine concentration throughout its hydrolysis reversible prevention within acetylcholinesterase [4]. The asetikolin transmission in central nerve system has a role in organizing the cognition functions, in particular to the attention and memory, which can be stimulated by the alpha-7 modulation inside the donepezil. The alpha-7 modulation nicotinic asetikolin of receptors have been considered as the objects of medications which are potential to treat the Alzheimer and schizophrenia [5].

In Indonesia, the assessment in determining the acuteness of schizophrenia patients before the presence of MoCA-Ina is conducted by performing weekly tests based on the Positive and Negative Syndrome Scale (PANSS) [6]. A study conducted by Friedman has reported that random consumption of donepezil was able to reduce the cognitive dysfunctions within the learning trial aspects in the form of California Verbal Learning Test, and the patients involved showed steady PANSS scores [7]. Meanwhile, another double-blind placebo-controlled trial study in the United States which involved both male and female patients with ages between 18 and 55 in 12 weeks has reported that the increase dosages of donepezil from 5 to 10 mg resulted in significant neurocognitive levels around $p < 0.05$ based on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [8]. On the other hand, Choi et al., has reported in Japan that the increasing of cognitive functions under consumption of donepezil, galantamine, and rivastigmine was obtained with significant level of parameters of verbal learning and memory (d = 2.3; $p = 0.06$; 95%CI – 0.01 to 0.46) [9].

The MoCA assessment is used to detect the light cognitive dysfunctions in any conditions including Alzheimer, Vascular Cognitive Impairment, Parkinson, Lewy body, frontotemporal dementia, multiple sclerosis, Huntington, brain tumor, ALS, sleep apnea, heart failure, drugs abuse, schizophrenia, HIV and head trauma [10], [11]. The Indonesian version of MoCA is a sensitive instrument in screening the Mild Cognitive Impairment (MCI) which is based on the original version from Canada, implying highly to culture differentiations to Indonesia. Nevertheless, the validity and reliability tests must be conducted earlier, so that the MoCA-Ina assessment is more accurate to be conducted in assessing the cognitive impairments than those from the original version or other types of assessments. For schizophrenia patients, the Mini-Mental State Examinations (MMSE) is a common method to be conducted [12]; however, this method has a lower number of examination tests in memory assessments than those from MoCA-Ina, which take a longer time to be done due to the involvement of executive tests, such as trial making test B; more complex language ability, more attention and abstract tests, more complex visuospatial in form of 3-dimension [13].

The prescription of risperidone with the additions of donepezil is expected to increase the cognitive dysfunctions of schizophrenia patients due to its ability in accelerating the thinking process, attention and awareness, working memory, visual and memory learning, verbal and memory learning, solving methods, and verbal understanding. The measurement by using the MoCA-Ina is more sensitive and understandable for Indonesian patients than those by using the original version of MoCA.

Material and Methods

Population and demographical studies

This research is a pre-post-test design experimental non-randomized with non-probability of consecutive sampling. The samples were collected based on the Dr Pirngadi Medan, Indonesia hospital. After receiving the local ethical committee clearance, male patients who have qualified the inclusion and exclusion criteria [12] are obtained. To determine the administration of the drug, the samples were divided into two groups for this study, and all of the samples were enrolled with written consent. Group I is 24 males schizophrenia patients who have been prescribed with risperidone and donepezil, while group II is 24 males schizophrenia patients who have been given only risperidone medication. The numbers of samples were appropriated to the sample formula for numerical scale calculation of unpaired groups, based on the literature review in Indonesia [13].

The samples collecting were conducted at RSUP Dr Pirngadi Medan, Sumatera Utara province, Indonesia from November 2017 to April 2018. The samples were diagnosed based on diagnostic criteria and structured interviews of Mini ICD 10 after being interviewed and asked to fill the informed consent.

The inclusion criteria were male schizophrenia patients with ages between 20 and 45; duration of illness 5 to 10 years limited to determine the relationship of the duration to cognitive ability; acute phase of assessment based on PANSS with score 60-80; antipsychotic medication is risperidone; normal body mass index (BMI IMT 18.50-24.99); two categories of education levels which are senior and junior high school. Moreover, the adjustment of MoCA-Ina score to every subject is decreasing as its score is below 26 (MoCA-Ina < 26). All of the subjects behaved cooperatively to be included in this research. Meanwhile, the exclusion criteria were all male schizophrenia patients with comorbidity of common diseases, organic mental or psychiatric disorders, and drugs abuse history except smoking and caffeine.

In this study, these two groups were prescribed with a fixed dose of risperidone (4 mg/day/orally), divided into two dosages, whereas the intervention group was prescribed with 5 mg/day/orally of donepezil in the night before sleeping until six weeks. Then the dosage of donepezil was increased from 5 mg to 10 mg per day orally at night until the week of 12 for 24 patients, and for the other subjects, the prescription given was only fixed dosages accounted for 4 mg/ day orally for 12 weeks.

The MoCA-Ina assessments were performed two times between 0 week and 12 weeks. The first assessment was done at six weeks after the medication has been prescribed, as well as the second assessment, which was conducted at 12 weeks (illustrated by Figure 1). This study involved on-treatment analysis, so as long as the drop out events occurred, the subjects were replaced directly. The drop out criteria is subjects which disobeyed to consume the medication or resigning to be included in the assessment.

MoCA-Ina administration and scoring

The MoCA-Ina is designed as screening instruments in determining light cognitive dysfunction. In assessing the different cognitive domains, i.e. attention, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculation and orientation, the time needed is around 10 minutes with total score 30 points; 26 or above is considered as normal [14], [15]. The MoCA has been validated in Indonesia language by Husein et al. in 2009 known as MoCA-Ina. The assessment based on MoCA-Ina consists of eight stages: visuospatial ability/executive (dimensions and shapes understanding), naming (naming animals' images), memory (memory measurement), attention (replaying the numerical rows), language (ability in using the language within sentences), abstraction (ability in using abstract), assessing the similarities of nouns, delayed recall (the ability in memorizing words without guidance), and orientation (the ability of orientation in understanding the years, months, days, dates, places, and cities [14]. The score assessment of MoCA-Ina is conducted in three times among week 0, 6, and 12.

Screening and assessment of cognitive impairment

The research subjects which have been recruited are those who have MoCA-Ina score below 26 (< 26). This score indicates that the subjects showed decreasing of cognitive functions based on the total for 30. The assessments which have been conducted to determine eight domains of cognitive functions to schizophrenia patients are attention/ awareness, verbal and memory learning, visual and memory learning, logic and solving problems, processing speed, verbal fluency, working memory, and social cognition.

Statistical analysis

The analysis performed in this study used the Chi-Square and Mann Whitney U analysis in addition to compare two groups based on demographical characteristics. The results of this study are analysed based on ages, occupations, education levels, marital status, duration of illness, initial disease, body mass index, smoking habits, PANSS scores of weeks 0, and an initial score of MoCA-Ina. To determine the pairing groups of male schizophrenia patients who have been prescribed with risperidone with the addition of donepezil at week 12, the T based on pairing group test was performed provided that it meets the test requirements; otherwise the data would be transformed followed by Wilcoxon test. Whereas the data of unpaired groups at week 12 were validated by using the unpaired T-test, followed by data transformation and Mann Whitney-U test respectively if the test requirement is not available. The value of *p* obtained is less than 0.001, indicating significant results, with data analysis performed by SPSS version 21.

Results

Enrolment

This research is the first study conducted in Sumatera Utara province regarding the MoCA-Ina score for male schizophrenia patients who have been prescribed by risperidone and donepezil. The subjects were recruited for 48 patients, divided into 2 groups, respectively for 24 individuals. The group I was those who have consumed risperidone and donepezil, while group II was those who have only been given with risperidone. In this study, no subjects were categorised as drop out criteria, suggesting no experiences of side effects of both medications during

consumption. The average ages for these two groups are 31.38 ± 4.78 (Group I), and 31.42 ± 4.68 (Group II).

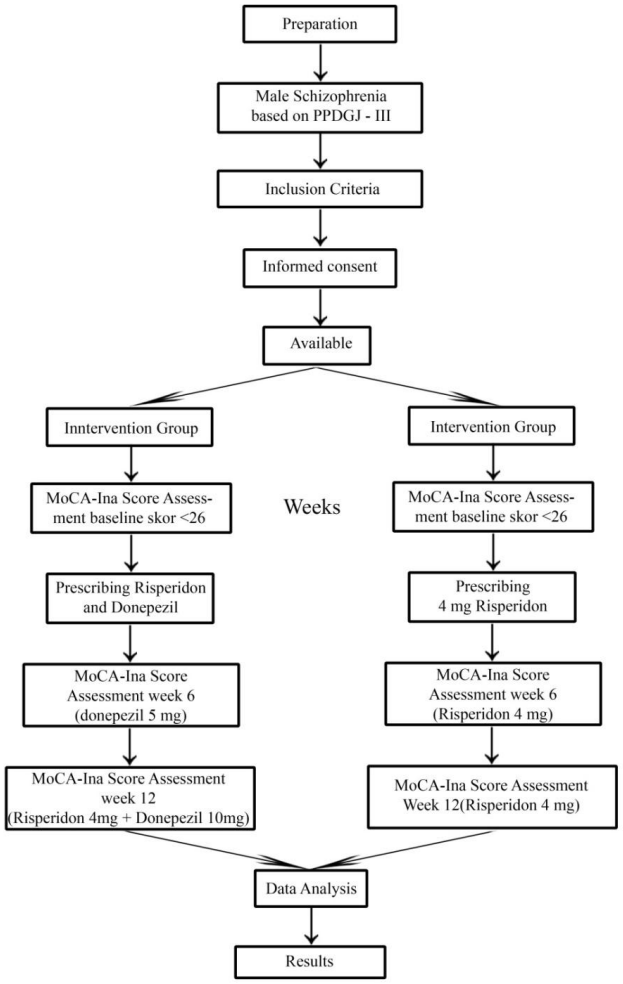

Figure 1: The flowchart of MoCA-Ina Assessment to male schizophrenia

Social demographic

The demographical data for the two groups of subjects are illustrated by the following Table 1. Based on the data, there are no differences of demographical characteristics within these groups, so that the subjects are valid based on the risperidone and donepezil prescriptions. The subjects were described as the level of educations accounted 17 people for junior high school, while 7 people were a senior high school for group I. On the other hand, group II was consisted by 18 people graduated from junior high school, and 6 people were graduated from senior high school. This demographical data provided that almost half of both groups I and II were accounted for unemployment, respectively 17 (47%) and 19 (52%). According to the healthy status, group I and II had similarity in the onset of illness duration around 24 ± 4.3 for a group I, and 23.83 ± 3.7 for group II, while the duration of illness for both groups was around 6.67 and 6.58 respectively. The similarities of demographical data were also found both in body mass index accounted for approximately 22 and smoking status around 13 ± 2.

Table 1: Demographical characteristics of subjects

Variable	Group of risperidone and Donepezil treatment (n = 24)	Group of risperidone treatment (n = 24)	*P*
Age (years)	31.38 ± 4.78	31.42 ± 4.68	0.976
Education levels (%)			
Junior high school	17 (48.6%)	18 (51.4%)	1.000
Senior high school	7 (53.8%)	6 (46.2%)	
Duration of Illness (years)	6.67 ± 1.606	6.58 ± 1.530	0.898
Onset of illness duration (years)	24.67 ± 4.331	24.83 ± 3.738	0.656
Initial score of MoCA-Ina	19.67 ± 2.200	19.92 ± 2.104	0.707
Body mass index	22.89 ± 0.940	22.69 ± 1.123	0.445
Occupations			
Employment	7 (58.3%)	5 (41.7%)	0.740
Unemployment	17 (47.2%)	19 (52.8%)	
Smoking	12.58 ± 2.165	13.33 ± 2.408	0.292
Marital Status			
Married	4 (44.4%)	5 (55.6%)	1.000
Unmarried	20 (51.3%)	19 (48.7%)	

MoCA-Ina Score

In this study, an initial score of MoCA-Ina was conducted for every group at the beginning of the week. The group I which has been prescribed with both risperidone and donepezil had an initial score for 19.67 with standard deviation (SD) 2.2, whereas the group II who has only given risperidone medication had an initial score for 19.92 with SD 2.1. The average score of MoCA-Ina to schizophrenia patients who have taken both risperidone and donepezil was 21.00 with SD 2.0, while the other scores who were given by only risperidone were averagely 20.45 with SD 1.9 after weeks sixth. Both groups I and II had MoCA-Ina score 22.83 (SD 1.65) and 21.25 (SD 1.93) respectively, which are illustrated in Table 2.

Table 2: Initial and final score of MoCA-Ina of research subjects

Time of assessment	*p-value*
Week 0 (risperidone + 0 mg donepezil)	19.66 ± 2.20, < 0.001, n = 24
Week 6 (risperidone + 5 mg donepezil)	21.00 ± 2.06, < 0.001, n = 24
Week 12 (risperidone + 10 mg donepezil)	22.83 ± 1.65, < 0.001, n = 24
Week 0 (risperidone)	19.91 ± 2.10, < 0.001, n = 24
Week 6 (risperidone)	20.45 ± 1.97, < 0.001, n = 24
Week 12 (risperidone)	21.25 ± 1.93, < 0.001, n = 24

Table 2 shows the differences between MoCA-Ina scores for research subjects during weeks 0, 6, and 12. Initial scores of every subject were almost the same accounted for 19.6 and 19.9. However these numbers increased slightly different to 21.0 and 21.5 respectively. This implies the addition of donepezil as medications had a small impact on the cognitive functions. Interestingly, the *p*-value of MoCA-Ina increased for subjects prescribed with higher dosages of donepezil (10 mg) to 22.5 while the non-consumed donepezil patients showed small decreasing to 21.2. The increasing of MoCA-Ina based on the donepezil consumption shows that the drugability in improving the cognitive functions of schizophrenia patients. This drug works in the cholinergic path, which can repair the cognitive dysfunctions as well as donepezil. In the schizophrenia patients, the cholinergic receptor deficit

occurs due to the presence of cholinesterase inhibitors that prevent the process, which can be reduced by donepezil by preventing the inhibitors [15]. In the meantime, the increase of average scores of MoCA-Ina after the addition of donepezil medication for 12 weeks occurred twice between week 0 to 6 and 6 to 12, in contrast for a prescription without donepezil addition increased only in week 0 to 6, and decreased in a very small number after week 6. The following Figure 2 displays the inclining trends of MoCA-Ina scores for donepezil medications.

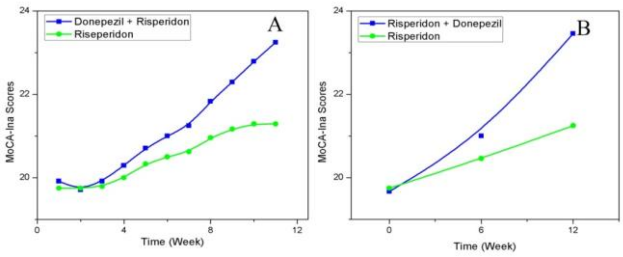

Figure 2: The increasing of average MoCA-Ina scores (A) the increasing trends in every week; (B) the comparison of exponential and linear increasing

Figure 2 illustrates the different patterns of inclining trends for every subject of research. The Figure 2(A) shows that the addition of risperidone and donepezil increased the scores for almost every week which had exponential pattern showed Figure 2(B), while the risperidone medication had a gradual increase of MoCA-Ina scores illustrated by the linear trend in Figure 2(B). This suggests that the addition of donepezil was able to improve the cognitive functions of male schizophrenia patients.

To every subject of the research illustrated in groups (Table 1), the demographical characteristics showed no significant differences as they are depicted with homogeneity of demographics. These phenomena suggest that there are significant results of male schizophrenia patients who have been prescribed with a combination of donepezil and Risperidone to those without the addition of donepezil. According to Figure 1 and 2, the data show a different increase of MoCA-Ina scores within week 6 and 12, which depict higher increasing for them with consumption of Risperidone and donepezil.

Discussion

According to Table 1, the demographical characteristics from every subject and the results showed no significant differences among them. In this study, subjects were divided into two groups, with an equal population of 24 patients. Group, I was prescribed with the combination of risperidone and donepezil, and the group II was given with only risperidone, which both of them were prescribed for 12 weeks. From the results, significant differences in particular of the increase of MoCA-Ina scores were obtained.

The results of this study are appropriate to those who have been reported by Zhu, Lee, Keefe, and Friedman. All of the studies showed similar increasing trends for 12 weeks with $p \leq 0.001$ [15]. Lee et al. have reported that the significant number was obtained with $p < 0.05$, whereas Keefe has concluded with the exact p score. Friedman which conducted the study in New York has reported significant results in the decrease of cutoff secondary memory and cognitive functions as well as reports which have been obtained by Choi in Japan with significant measurement due to the results of verbal learning and memory with $p = 0.06$. In this study, the results showed the increasing of MoCA-Ina scores at week 6 and 12 with p-value < 0.013. The results of this study which have similarity to the previous studies suggest that the Indonesian version of MoCA can be considered as the references in assessing the cognitive functions of male schizophrenia patients. Interestingly, the MoCA-Ina assessments are more appropriate than those from the original versions because of the language used in which provide a better understanding of the Indonesian male schizophrenia patients. This also implies to the education levels of the subjects which graduated from secondary schools.

To be concluded, in DSM 5, the schizophrenia medications with the prescribing of 4 mg risperidone can increase the MoCA-Ina scores. However, the inclining is in slight trend. Therefore, the addition of donepezil is expected to improve the cognitive functions of male schizophrenia patients significantly based on the scores of MoCA-Ina.

Acknowledgement

The author would like to thank the director of Dr Pirngadi Hospital Medan, and the head of Psychiatry Department of Dr Pirngadi Hospital Medan, North Sumatera.

References

1. Tamingga C. Schizophrenia and Other Psychotic Disorders. In: Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock Comprehensive Textbook of Psychiatry, 9th editio., New York: Lippincott Williams & Wilkins, 2009:1433-7.

2. Goff DC, Hill M, Barch D. The treatment of cognitive impairment in schizophrenia. Pharmacology Biochemistry and Behavior. 2011; 99(2):245-53. https://doi.org/10.1016/j.pbb.2010.11.009 PMid:21115035 PMCid:PMC3114283

3. Penadés R, Pérez-García H, González-Rodríguez A, Catalan R, Bernardo M. Treating cognition in schizophrenia: searching for the best evidence-based practices. Evidence-based Psychiatr Care. 2016:80-84.

4. O.D. Tablets, ARICEPT® (Donepezil Hydrochloride Tablets). pp. 3-30.

5. Zhu W, Zhang Z, Qi J, Liu F, Chen J, Zhao J, Guo X. Adjunctive treatment for cognitive impairment in patients with chronic schizophrenia: a double-blind, placebo-controlled study. Neuropsychiatric disease and treatment. 2014; 10:1317. https://doi.org/10.2147/NDT.S64189 PMid:25075190 PMCid:PMC4106965

6. Opler LA, Medalia A, Opler MG, Stahl SM. Pharmacotherapy of cognitive deficits in schizophrenia. CNS Spectr. 2014; 19(2):142-156. https://doi.org/10.1017/S1092852913000771 PMid:24229725

7. Keefe RS, Malhotra AK, Meltzer HY, Kane JM, Buchanan RW, Murthy A, Sovel M, Li C, Goldman R. Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology. 2008; 33(6):1217-28. https://doi.org/10.1038/sj.npp.1301499 PMid:17625502

8. Friedman JI, Adler DN, Howanitz E, Harvey PD, Brenner G, Temporini H, White L, Parrella M. A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for the cognitive impairment of schizophrenia. Biological psychiatry. 2002; 51(5):349-57. https://doi.org/10.1016/S0006-3223(01)01342-7

9. Choi KH, Wykes T, Kurtz MM. Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy. The British Journal of Psychiatry. 2013; 203(3):172-8. https://doi.org/10.1192/bjp.bp.111.107359 PMid:23999481 PMCid:PMC3759029

10. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005; 53(4):695-9. https://doi.org/10.1111/j.1532-5415.2005.53221.x PMid:15817019

11. Tiffin-Richards FE, Costa AS, Holschbach B, Frank RD, Vassiliadou A, Krüger T, Kuckuck K, Gross T, Eitner F, Floege J, Schulz JB. The Montreal Cognitive Assessment (MoCA)-a sensitive screening instrument for detecting cognitive impairment in chronic hemodialysis patients. PloS one. 2014; 9(10):e106700. https://doi.org/10.1371/journal.pone.0106700 PMid:25347578 PMCid:PMC4209968

12. Sastroasmoro S, Ismael S. Dasar-dasar metodologi Penelitian Klinis, edisi ketiga. CV Sagung Seto, Jakarta. 2008.

13. D MS, Uji hipotesis komparatif numerik berpasangan. Dalam statistic untuk kedokteran dan kesehatan, deskriptif, bivariat, dan multivariat dilengkapi aplikasi SPSS, Edisi Keenam. Jakarta: Epidemilogi Indonesia, 2015.

14. Husein N, Lumempouw S, Ramli Y, Herqutanto H. Uji Validitas Dan Reliabilitas Montreal Cognitive Assessment Versi Indonesia (Moca-Ina) Untuk Skrining Gangguan Fungsi Kognitif, 2009.

15. Pae C-U. Role of the cholinesterase inhibitors in the treatment of schizophrenia. Expert Opin Investig Drugs. 2013; 22(3):293-298. https://doi.org/10.1517/13543784.2013.762355 PMid:23330829