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Short Communication

Motor improvement in Parkinson's disease patients receiving caffeine adjuvants: A double-blind randomized controlled trial in Indonesia

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Abstract

Parkinson's disease (PD) manifests as a movement and brain function disorder characterized by symptoms such as resting tremors, rigidity, bradykinesia, and postural instability, leading to disability among patients. The use of psychostimulants such as caffeine has been associated with the improvement of motor symptoms in PD patients; however, studies regarding the effect of caffeine adjuvant therapy on motor function among PD patients in the Indonesian population are lacking. The aim of this study was to evaluate motor improvement as measured by the change in scores of the Movement Disorder Society - Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III) among PD patients receiving caffeine adjuvant. A double-blind randomized controlled trial (RCT) was conducted among PD patients at Dr. Soetomo General Academic Hospital and Universitas Airlangga Hospital, Surabaya, Indonesia, from April to August 2023. A total of 27 patients were enrolled and randomly assigned to an intervention (receiving caffeine adjuvant, n=15) and control group (receiving placebo, n=12). Motor improvement was measured using the UPDRS III score prior to intervention and three weeks after. The Chi-squared test was used to analyze the difference in UPDRS III scores between the two groups. Motor improvement, as demonstrated by a reduction in the UPDRS III score, was observed in patients receiving caffeine adjuvant compared to those receiving placebo (80.0% vs 16.7%; p=0.004). Regarding the safety profile, only four out of 15 (26.6%) patients treated with caffeine reported minor adverse events. These conditions improved over time during the intervention. None of the 12 patients in the placebo reported adverse events. This study provides valuable insights into the initial dosage of caffeine that improves motor function in PD patients with minimum adverse effects.

Keywords: Parkinson's disease, UPDRS III, adjuvant therapy, caffeine, motor improvement

Introduction

Parkinson's disease (PD) is one of the most common movement disorders caused by basal ganglia degeneration in the substantia nigra pars compacta cells. It is characterized by symptoms such as tremor at rest, rigidity, bradykinesia, and postural instability [1]. In 2016, the global number of PD cases reached 6.1 million worldwide, marking a 2.4-fold increase from 1990's 2.5 million cases [2]. The prevalence is projected to rise, reaching approximately 8.7 million people in 2030 due to the growing elderly population [3,4]. Indonesia estimates approximately 876,665

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cases out of its 238,452,952 total population, ranking 12th globally or 5th in Asia for PD-related deaths, with a prevalence of 1100 deaths in 2002 [5].

PD often leads to disability among patients, which is caused primarily by the manifestation of motor symptoms [2]. To assess the clinical course of PD, various clinical assessment scales have been employed, including the Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS has been recognized as an international benchmark clinical grading standard for PD [6], and consists of six sub-scales each for the assessment of intellectual and mood disorders (UPDRS I); daily activities (UPDRS II); motor function (UPDRS III); therapy complications (UPDRS IV); Hoehn and Yahr (HY) staging; and Schwab and England (SE) activities of daily living score [6,7].

Various supportive treatment options for PD have been introduced, including the use of caffeine [8]. A study in rat and mouse models of PD showed that caffeine might counteract symptoms and enhance the therapeutic effects of L-dopa, along with its neuroprotective properties that prevented damage to dopaminergic cells in the animal models [9]. Other clinical studies showed promising results of motor function improvement among PD patients after receiving caffeine, including improvement in the UPDRS III score [10], overall UPDRS score [11], and improved gait akinesia [12]. However, there is no study within the Indonesian population regarding the effect of adjunct caffeine administration on motor improvement in PD patients, highlighting the need for further investigation and data gathering in this area. The aim of this study was to determine the effect of adjuvant caffeine on motor improvement, as measured by the UPDRS III score changes, among PD patients in the Indonesian population.

Methods

Study population, design, and settings

A double-blind randomized controlled trial (RCT) was carried out among PD patients at Dr. Soetomo General Academic Hospital and Universitas Airlangga Hospital, Surabaya, Indonesia, from April to August 2023. Using a consecutive sampling technique, patients who met the inclusion criteria were enrolled after being previously informed of the study and provided written consent. The inclusion criteria were PD patients in outpatient clinic receiving symptomatic therapy with a stable regimen for a minimum of three months. Meanwhile, patients with gastrointestinal disorders, epilepsy or a history of seizures, and uncontrolled hypertension; diagnosed with supra ventricular tachycardia or arrhythmia; receiving different drug regimens within the past three months; and having a history of pallidotomy or deep brain stimulation were excluded. The participants were dropped out once they consumed food or beverages containing caffeine, experienced seizures, failed to take the provided caffeine adjuvant within 24 h, and refused to continue the intervention.

Sample size determination and randomization

The sample size was determined using a two-sample proportion formula. The critical value of normal distribution at the desired level of significance (α=0.05) of 1.96, 80% power of 0.84, estimated proportion in the intervention group of 20%, estimated proportion in the control group of 80% and the ratio of the sample sizes between the two groups (r) of 1 yielded the required minimum total sample of 20, with 10 samples in each group.

A total of 27 participants fulfilling the inclusion and exclusion criteria were recruited from both hospitals for randomization. The participants were randomly assigned to either the intervention or control group by pharmacists at the respective hospitals. The investigators were blinded to group allocation and the participants were unaware of their group as both groups received the same appearance of pills.

Study variables and data collection

This study assessed the effect of caffeine adjuvant therapy (as an independent variable) on motor improvement among PD patients, determined by the changes in UPDRS III score (as a dependent variable). The caffeine used was pharmaceutical grade caffeine adjuvant as anhydrous-crystalline powder (CSPC Innovation Pharmaceutical Co., Shijiazhuang, China). Other data such as patients' demographic characteristics (age and gender), clinical profiles (comorbidities, medication

consumption, heart rates, and blood pressure), as well as the history of caffeinated drink consumption were also recorded. Age, gender, comorbidities, and drug consumption were included in the assessment of confounding variables of the study.

The data were collected by the researcher through anamnesis, physical examinations, and neurological assessment before and after the intervention. The UPDRS III scores were calculated using the UPDRS III scoring instrument. Patients' compliance with caffeine medication was ensured through regular follow-up, and medication adherence was evaluated through medical history inquiries and daily logs of patients' medication intake during post-caffeine therapy check-ups.

Experimental setup

The enrolled participants were randomly divided into the intervention and control group, consisting of 15 and 12 participants, respectively. The difference in the number of participants between the two groups was due to the technical provision of drugs, as well as the different number of participants obtained at each hospital. Patients in the intervention group were treated with caffeine adjuvant, whereas those in the control group received a placebo containing 50 mg amylum (caffein-free), along with main PD symptomatic therapy. Either caffeine or placebo was given at a dose of 2×50 mg/day, orally, after breakfast and dinner for three weeks. Each type of drug was prepared in capsules (50 mg/capsule) by hospital pharmacists before being given to the participants. Before the intervention, each participant was instructed to refrain from consuming beverages containing caffeine (e.g., coffee, tea, chocolate, chocolate milk, soft drinks, carbonated drinks, and caffeinated energy drinks) a week prior to, during, and a week after the intervention period. The baseline UPDRS III score was calculated for each patient and the procedure was repeated after the intervention to evaluate the effect of caffeine adjuvant administration on motor improvement.

UPDRS III scoring and motor improvement assessment

UPDRS III scoring scale was used to assess the manifestations of motor symptoms in the participants. It involves 14 different categories: speech, facial expression, resting tremor, postural tremor on hands, rigidity, finger taps, hand movement, rapid alternative movement of hands, leg agility, arising from a chair, posture, gait, postural instability, and bradykinesia and hypokinesia. Each category consists of a different number of observation items, ranging from 1 to 5, yielding a total of 27 observation items. The score for each category ranges from 0–4, yielding a total score ranging from 0–108. The scoring details are as follows: 0=normal (no motor symptom involvement), 1–27=mild disorder, 28–54=moderate disorder, 55–81=severe disorder, and 82–108=very severe disorders [7]. Tremor amplitude on the extremities was evaluated by estimating deviations of tremor on fingers and toes in centimeters in accordance with the UPDRS III guideline.

The assessment of motor improvement was carried out by four competent and well-trained neurology–movement disorder doctors. A reduction in the UPDRS III score of >4 points after the intervention, as compared to the baseline examinations, indicated a significant motor improvement. On the other hand, no alteration in the UPDRS III score, a reduction of <4 points, or an increase in the UPDRS III score as compared to the early assessment indicated no motor improvement.

Statistical analysis

Data on demographic and clinical characteristics were analyzed using descriptive statistics and presented as percentage (%) and mean±standard deviation (SD). Chi-squared test was performed to compare UPDRS III scores between the control and treatment groups, and logistic regression analysis was carried out to determine the effect of confounding variables on motor improvement. A p-value of <0.05 was considered statistically significant. All data analyses were performed using SPSS software version 20 (IBM, New York, USA).

Results

Participants' demographic characteristics and comparative analysis

In total, 27 patients (12 from Dr. Soetomo General Academic Hospital and 15 from Universitas Airlangga Hospital) were included in the study, comprising 12 (44.4%) males and 15 (55.6%) females. None of the participants dropped out during the intervention process. The participant's characteristics and clinical profile are summarized in **Table 1**. The majority (59.3%) of the participants were aged >60 years, and almost half (48.1%) presented with comorbidities (i.e., hypertension and diabetes mellitus). Fifteen participants (55.6%) were under the treatment of levodopa, carbidopa, and entacapone; 12 (44.4%) had levodopa in combination with benserazide; 10 (37.0%) consumed pramipexole; and 10 (37.0%) received trihexyphenidyl therapy. Four out of 15 (26.6%) participants in the treatment group reported adverse effects such as heart palpitations, frequent urination, difficulty sleeping, and anxiety during early caffeine therapy; however, the complaints improved over time during the intervention period. Based on the baseline UPDRS III score, the majority (70.4%) of the participants had mild motoric symptoms, whereas the rest showed moderate-severe symptoms.

A comparative analysis at baseline revealed no statistically significant differences between the two groups in terms of age, gender, comorbidities, drugs consumption, and adverse effects (all had $p>0.05$), justifying an overall equivalent subject distribution between the two groups. However, in the course pre-UPDRS III categories, data distribution varied significantly between the caffeine and placebo groups ($p=0.043$) (**Table 1**).

Table 1. Comparison of participants' demographic and clinical characteristics at baseline, n=27

Variable	Treatments, n (%)		Total (n=27)	*p*-value
	Caffeine adjuvant (n=15)	Placebo (n=12)		
Gender				
Male	5 (33.3)	7 (58.3)	12 (44.4)	0.363[a]
Female	10 (66.7)	5 (41.7)	15 (55.6)	
Age (year), mean±SD	60.47±10.54	60.75±11.80	60.59±10.90	
>60	9 (60.0)	7 (58.3)	16 (59.3)	1.000[b]
<60	6 (40.0)	5 (41.7)	11 (40.7)	
Comorbidities				
Hypertension	2 (13.3)	6 (50.0)	8 (29.6)	0.087[b]
Diabetes mellitus	2 (13.3)	3 (25.0)	5 (18.5)	0.628[b]
Drugs consumed				
Levodopa, carbidopa, entacapone	7 (46.7)	8 (66.7)	15 (55.6)	0.516[a]
Levodopa, benserazide	9 (60.0)	3 (25.0)	12 (44.4)	0.153[a]
Pramipexole	6 (40.0)	4 (33.3)	10 (37.0)	1.000[b]
Trihexyphenidyl	7 (46.7)	3 (25.0)	10 (37.0)	0.424[b]
Adverse effects				
Yes	4 (26.6)	0 (0.0)	4 (14.8)	0.106[b]
No	11 (73.3)	12 (100)	23 (85.2)	
Types of adverse effects				
Frequent urination	1 (6.7)	0 (0.0)	1 (3.7)	
Difficulty sleeping	1 (6.7)	0 (0.0)	1 (3.7)	0.440[a]
Heart palpitations	1 (6.7)	0 (0.0)	1 (3.7)	
Anxiety	1 (6.7)	0 (0.0)	1 (3.7)	
Pre-caffein UPDRS III categories				
Mild	8 (53.3)	11 (91.7)	19 (70.4)	0.043*[b]
Moderate - severe	7 (46.7)	1 (8.3)	8 (29.6)	

[a] Analyzed using a Chi-squared test
[b] Analyzed using a Fisher's exact test
*Statistically significant at $p<0.05$

Analysis of confounding variables associated with motor improvement

Several factors were assessed to identify possible potential confounders associated with motor improvement. In univariate analysis, gender, age, and comorbidities were not significantly associated with motor improvement ($p>0.05$), whereas trihexyphenidyl consumption was significantly correlated with motor improvement ($p=0.046$) (**Table 2**), suggesting that trihexyphenidyl may serve as a confounding variable in the study. Nevertheless, in multivariate

analysis controlling for trihexyphenidyl and caffeine, caffeine therapy was the only factor significantly associated with motor improvement, with 25 times higher odd as compared to trihexyphenidyl (95%CI: 2.323–269.067; p=0.008). The same result was also noted when assessing early UPDRS III score and caffein therapy in association with motor improvement, in which UPDRS score at baseline had no association with motor improvement (p>0.05) (**Table 3**).

Table 2. Bivariate analysis showing factors associated with motor improvement

Variables	Motor improvement, n (%)		Total (n=27)	p-value
	Yes (n=14)	No (n=13)		
Gender				
Male	7 (50.0)	5 (38.5)	12 (44.4)	0.830
Female	7 (50.0)	8 (61.5)	15 (55.6)	
Age (year), mean±SD				
>60	8 (57.1)	8 (61.5)	16 (59.3)	1.000[a]
<60	6 (42.9)	5 (38.5)	11 (40.7)	
Comorbidities				
Hypertension	3 (21.4)	5 (38.5)	8 (29.6)	0.420
Diabetes mellitus	2 (14.3)	3 (23.1)	5 (18.5)	0.648
Drugs consumed				
Levodopa, carbidopa, entacapone	7 (50.0)	8 (61.5)	15 (55.6)	0.830 [a]
Levodopa, benserazide HCl	7 (50.0)	5 (38.5)	12 (44.4)	0.830 [a]
Pramipexole	6 (42.9)	4 (30.8)	10 (37.0)	0.695[b]
Trihexyphenidyl	8 (57.1)	2 (15.4)	10 (37.0)	0.046*[b]

[a] Analyzed using a Chi-squared test
[b] Analyzed using a Fisher's exact test
*Statistically significant at p<0.05

Table 3. Multivariate logistic regression analysis showing factors associated with motor improvement

Factor	Unstandardized beta (B)	OR (95%CI)	p-value
Trihexyphenidyl	2.303	10.00 (0.80–123.99)	0.073
Caffeine	3.219	25.00 (2.32–269.06)	0.008*
Baseline UPDRS III score	-1.802	0.16 (0.01–2.21)	0.174
Caffeine	2.622	13.71 (1.74–108.24)	0.013*

*Statistically significant at p<0.05

Association between caffeine adjuvant therapy and motor improvement

Approximately 80.0% of the patients receiving caffeine therapy exhibited motor improvement. Meanwhile, only 16.7% of the participants exhibited motor improvement after the treatment with a placebo. The result of Chi-squared analysis suggested patients treated with caffeine had a 20 times higher odd of experiencing motor improvement as compared to those receiving placebo (95%CI: 2.77–144.31) (**Table 4**).

Table 4. Association between caffeine adjuvant administration and motor improvement

Treatment	Motor improvement, n (%)		Total	OR (95%CI)	p-value
	Yes (n=14)	No (n=13)			
Caffeine	12 (80.0)	3 (20.0)	15	20.00 (2.77–144.31)	0.004*
Placebo	2 (16.7)	10 (83.3)	12		

*Statistically significant at p<0.05

We also performed additional calculations to predict several important events associated with caffeine administration (**Table 5**). Based on event rates (failure to improve motor function) calculations, the experimental event rate was 20.0%, and the control event rate was 83.3%. Caffeine lowered the risk of motor improvement failure by 63.3% (absolute risk reduction 0.633), and a higher percentage (76.0%) of risk reduction was noted when compared to the control group (relative risk reduction 0.76). Additionally, to prevent one patient from not having motor improvement, two patients need to be treated with caffeine therapy (number needed to treat (NNT) 2). Furthermore, caffeine administration at a dose of 100 mg/day would give a patient 1.5 times likelihood to experience improved motor function instead of undesirable effects (likelihood to be helped or harmed (LHH) 1.5) (**Table 5**).

Table 5. Predictions of events associated with motor improvement after caffeine therapy

Indicators	Equation	Value	% (95%CI)
Experimental event rate (EER)		3/15=0.20	20.0
Control event rate (CER)		10/12=0.833	83.3
Absolute risk reduction (ARR)	CER–EER	0.833–0.20=0.633	63.3 (34.1–92.5)
Relative risk reduction (RRR)	ARR/CER	0.633/0.833=0.76	76.0 (41–100)
Number needed to treat (NNT)	1/ARR	1–0.633=2	
Likelihood to be helped or harmed (LHH)	NNH/NNT	3/2=1.5	

Adverse effects and several important events associated with caffeine therapy

Four out of 15 (26.0%) patients in the intervention group reported adverse effects, suggesting that 33.0% of the patients receiving caffeine treatment experienced adverse effects (experimental event rate 0.33) (**Table 6**). On the other hand, none of the participants (0.0%) in the placebo group experienced side effects, resulting in a control event rate of 0.00. Based on these, patients undergoing caffeine treatment would have approximately 33.0% greater chance of developing side effects than those receiving placebo (absolute risk increase 0.33), indicating that 1 out of every 3 patients would experience adverse effects from caffeine adjuvant uptake (number needed to harm 3) (**Table 6**).

Table 6. Predictions of events associated with adverse effects from caffeine therapy

Indicators	Equation	Value
Experimental event rate (CER)		4/12=0.33
Control event rate (CER)		0/12=0
Absolute risk increase (ARI)	CER–EER	0–0.33=0.33
Number needed to harm (NNH)	1/ARI	1/0.33=3

Discussion

PD is a progressive brain disorder associated with dopaminergic neuron degeneration in the substantia nigra, leading to uncontrolled movements such as resting tremor, stiffness, slow movement, and postural imbalance [3]. Disability such as difficulty walking, eating, and talking may occur as the disease progresses [13]. Hence, it is imperative to implement strategies for the prevention and treatment of PD, including the use of adjuvant therapies. In the present study, we evaluated the association between caffeine adjuvant therapy and motor improvement among PD patients, assessed by changes in UPDRS III score. The patients' baseline characteristics between the intervention and control group were also compared to ensure the equality of frequency distribution, thus reducing bias in the study.

We found in our study that the majority of participants were aged >60 years. This was in accordance with previous studies, reporting that individuals above 60 years of age were more prone to PD [14-16], although uncommon cases in younger individuals have also been documented [17]. Alterations in neuronal circuitry and density, as well as increased neuronal inflammatory response, have been linked to an increased risk of developing PD in the elderly, leading to cognitive decline and olfactory dysfunction [18,19]. Additionally, older age has also been associated with functional and locomotor disability among the elderly [20,21]. In contrast to other studies suggesting that males are more susceptible to PD [22,23], our study recorded a higher percentage (55.5%) of female participants compared to males. This difference in ratio might be due to a small sample size adopted in the study and coincidentally more females fulfilling the inclusion criteria. However, at baseline assessment, the proportion of participants between the intervention and control groups was comparatively similar in terms of age, gender, comorbidities, drugs consumed, and adverse effects (p>0.05) (**Table 1**).

This study showed a significant improvement in motor function in patients receiving caffeine adjuvant therapy. Caffeine adjuvant therapy for 21 days (2×50 mg/oral daily) was able to reduce the UPDRS III score in 80.0% of the patients in the intervention group, whereas placebo at the same dose failed to improve motor function in more than 83.3% of the patients in the control group. Additionally, patients receiving caffeine treatment had a 20 times higher chance of experiencing motor improvement as compared to those taking a placebo (**Table 4**). This finding was in line with that reported in a previous study, suggesting that caffeine administration 100

mg/day had reduced the occurrence of freezing of gait [12]. Another study also reported that caffeine therapy 2×100 mg/oral daily had significantly improved motor function after three weeks of treatment [10].

Caffeine is a neuromodulator that acts as an antagonist of the adenosine-2A (A2A) receptor, indirectly impacting the activity of striatopallidal nerves [24]. This receptor colocalizes with dopaminergic D2 receptors as a heteromer, thereby inhibiting dopaminergic transmission [25]. In the presence of caffeine, the levels of intracellular cAMP and the release of GABA within the globus pallidus are reduced, whereas serotonin and noradrenaline in striatopallidal neurons are enhanced, thus resulting in enhanced motor performance. Additionally, caffeine stimulates dopamine D1 and D2 receptors, promoting increased uptake of glutamate into astrocytes and lowering glutamate levels in the synaptic cleft, potentially ameliorating motor symptoms and improving motor function in individuals with PD [8]. Caffeine was also reportedly able to enhance the bioavailability of levodopa and prolong its clinical effects. The clinical effect of caffeine can persist even after levodopa levels decline, indicating the importance of caffeine interaction with the D2 receptor [26].

To ensure that there were no other factors distorting the association between caffeine and motor improvement, several variables such as age, gender, comorbidities, and medication consumption were included in the assessment of potential confounders associated with motor improvement. Among these factors, THP consumption was the only factor associated with motor improvement ($p<0.05$) (**Table 2**). Nevertheless, in multivariate logistic regression analysis controlling for THP and caffeine, as well as UPRDS III score at baseline and caffeine, caffeine was the only factor significantly associated with motor improvement ($p<0.05$), and the patients receiving caffeine treatment were 25 times more likely to experience improved motor function compared to THP (**Table 3**).

We found that 4 out of 15 (26.6%) patients receiving caffeine therapy experienced adverse effects (i.e., heart palpitation, frequent urination, difficulty sleeping, and anxiety); however, these conditions improved over time during the intervention. A similar finding was reported in a previous study, indicating that 17.0% of the patients undergoing caffeine treatment experienced undesirable effects such as gastrointestinal disturbance, insomnia, anxiety, headache, frequent urination, nausea, and palpitation [10,27]. However, the effects of caffeine are dose-dependent and vary among individuals, in which doses of <400 mg are often associated with positive effects, whereas doses of >400 are often linked to undesirable effects [28].

This study possesses several limitations that should be discussed. The study was conducted only at two hospitals in East Java and confined to a relatively small population. Thus, the research subjects enrolled might not represent the overall characteristics of patients in a broader area. Caffeine administration was limited to a three-week duration, which precluded the assessment of adverse effects associated with long-term caffeine consumption. This study was unable to determine and monitor caffeine levels in the participants' blood before and after the intervention, as this data could have been valuable for dosage optimization, ensuring patient safety, assessing compliance, and evaluating pharmacokinetics. Thus, further research is warranted to address these limitations. However, this study represents the first double-blind RCT assessing the impact of caffeine adjuvant therapy on motor improvement, specifically within the Indonesian population, and provides significant insight into the initial caffeine dosage that augments motor function in PD patients with minimum adverse effects.

Conclusion

Our study demonstrated that the use of caffeine adjuvant was associated with motor improvement among PD patients, compared to those taking placebo. This study provides valuable insights into the initial dosage of caffeine that improves motor function in PD patients with minimum adverse effects. Further study with a longer intervention duration is necessary to evaluate sustained efficacy and potential long-term adverse effects of caffeine intake. Additionally, investigations to determine the optimal caffeine dosage tailored to the body weight of PD patients, as well as assessment of UPDRS III scores a month post-discontinuation of caffeine adjuvant therapy, are needed to confirm sustained motor improvement.

Ethics approval

This study was approved by the Health Research Ethical Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (0648/KEPK/IV/2023) and Universitas Airlangga Hospital (UA -01-23092).

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

All data are available as part of the article.

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References

1. Kalia LV, Lang AE. Parkinson's disease. Lancet 2015;386(9996):896-912.
2. Dorsey ER, Elbaz A, Nichols E, *et al*. Global, regional, and national burden of Parkinson's disease, 1990–2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurol 2018;17(11):939-953.
3. Syamsudin T. Pakinson Disease. In: Syamsudin T, Subagya, Akbar M, editors. Handbook for the management of Parkinson's disease and other movement disorders. edn. Jakarta: Indonesian Association of Neurologists; 2015.
4. Dewati E, Tunjungsari D. Buku ajar neurologi FKUI 2017. Jakarta: Kedokteran Indonesia; 2017.
5. Wikandikta IPG, Samatra DPGP, Meidiary AAA. Prevalensi gangguan tidur pada penderita parkinson di Poli Saraf RSUD Wangaya Denpasar tahun 2017. Intisari Sains Medis 2020;11(3):1085-1090.
6. Sari H, Harris S, Hakim M, Misbach Y. Perubahan fungsional penyakit Parkinson dengan menggunakan unified parkinson's disease rating scale (UPDRS). Neurona 2010;27(2):1-10.
7. Perlmutter JS. Assessment of Parkinson disease manifestations. Curr Protoc Neurosci 2009;49(1):10.1.
8. Roshan MH, Tambo A, Pace NP. Potential role of caffeine in the treatment of Parkinson's disease. Open Neurol J 2016;10:42-58.
9. Tran A, Zhang C, Cao C. The role of coffee in the therapy of Parkinson's disease. J Alzheimers Dis Parkinsonism 2015;5(3):2161-2460.
10. Postuma RB, Lang AE, Munhoz RP, *et al*. Caffeine for treatment of Parkinson disease: A randomized controlled trial. Neurology 2012;79(7):651-658.
11. Kauther KM, Höft C, Rissling I, *et al*. The PLA2G6 gene in early-onset Parkinson's disease. Mov Disord 2011; 26(13):2415-2417.
12. Kitagawa M, Houzen H, Tashiro K. Effects of caffeine on the freezing of gait in Parkinson's disease. Mov Disord 2007;22(5):710-712.
13. He L, Lee E-Y, Sterling NW, *et al*. The key determinants to quality of life in Parkinson's disease patients: Results from the Parkinson's disease biomarker program (PDBP). J Parkinsons Dis 2016;6(3):523-532.
14. Koleangan GM, Mawuntu AH, Kembuan MA. Karakteristik dan kualitas hidup pasien penyakit Parkinson dengan probabel gangguan perilaku tidur fase gerak mata cepat di Manado. e-CliniC 2020;8(1):120-126.

15. Tambun O, Marisdina S, Bahar E. Faktor-faktor yang mempengaruhi kualitas hidup penderita penyakit Parkinson dengan menggunakan Parkinson's disease questionnaire-39. Neurona 2021;38(4):270-276.
16. Hamdan M, Nugraha P, Librata PN, Cecilia C. Nonmotoric symptoms scale (NMSS) validity and reliability test in patients with Parkinson's disease in Dr. Soetomo General Hospital, Surabaya, Indonesia: A questioner validation study. Pharmacognosy Journal 2023;15(3):316-320.
17. Subiantoro R, Konginan A, Yulianti E. A 56 year old man with Parkinson's disease and depression: A case report on treatment management. Indian J Forensic Med Toxicol 2021;15(4):2273-2276.
18. Wood H. Severe olfactory dysfunction may herald cognitive decline in Parkinson disease. Nat Rev Neurol 2012;8(3):122.
19. Alves J, Petrosyan A, Magalhães R. Olfactory dysfunction in dementia. World J Clin Cases 2014;2(11):661-667.
20. Suyasa IGPD, Sutini NK, Kamaryati NP, Nuryanto IK. Determinant of functional disability in instrumental activities of daily living among elderly living in a rural area in Bali: A cross-sectional study. Jurnal Ners 2023;18(2):110-116.
21. Jain S, Khalique N, Ahmad S, *et al*. Locomotor disability among adult population of a North Indian district: A cross sectional study. The Indones J Public Health 2023;18(1):11-20.
22. Haeriyoko WA, Samatra DP, GS SYT, *et al*. Profil gangguan tidur penderita parkinson di rumah sakit rujukan di kota Denpasar Tahun 2018. Callosum Neurology 2020;3(1):12-16.
23. Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. Front Neuroendocrinol 2014;35(3):370-384.
24. Jenner P. Istradefylline, a novel adenosine A2A receptor antagonist, for the treatment of Parkinson's disease. Expert Opin Investig Drugs 2005;14(6):729-738.
25. Benarroch EE. Adenosine and its receptors: Multiple modulatory functions and potential therapeutic targets for neurologic disease. Neurology 2008;70(3):231-236.
26. Deleu D, Jacob P, Chand P, *et al*. Effects of caffeine on levodopa pharmacokinetics and pharmacodynamics in Parkinson disease. Neurology 2006;67(5):897-899.
27. Liveina A. Pola konsumsi dan efek samping minuman mengandung kafein pada mahasiswa program studi pendidikan dokter Fakultas Kedokteran Universitas Udayana. E-Jurnal Medika Udayana 2014;3(4):1-12.
28. Willson C. The clinical toxicology of caffeine: A review and case study. Toxicol Rep 2018;5:1140-1152.