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Clonazepam as Add-on Therapy in Parkinson's Patients with Sleep Disorders: A Prospective Pilot Study using Video Polysomnography

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Use of Clonazepam was very common in Parkinson's patient with sleep problems such as rapid eye movement behavior Disorder. A pilot study was performed to evaluate the effects of Clonazepam on sleep pattern in Parkinson's patient using video polysomnography. Overnight polysomnography was performed prospectively in three healthy males (age 51.33±3.51 years) and with three male Parkinson's patient (age 60.00±8.00 years) with sleep disorders. The study was conducted in two phases using standard techniques in accordance with guidelines published by the American Academy of Sleep Medicine (AASM). For sleep stages evaluation, an electroencephalogram (4 channels with 2 central and 2 occipital) chin electromyogram (with 1 channel) and electro-oculogram (with 2 channels) were achieved. Polysomnography characteristics of healthy volunteers and Parkinson's patient with and with out Clonazepam effect was evaluated. Sleep latency was compared between healthy volunteers and Parkinson's patients in both the phases. The difference was highly significant [Phase I ($p = 0.004$, $R^2 = 0.896$), Phase II ($p<0.001$, $R^2=0.999$)], but there was no considerable effect of Clonazepam in PD Patients [Phase I, ($p = 0.606$, $R^2=0.072$) Phase II ($p = 0.726$, $R^2 = 0.081$)]. Clonazepam significantly increases the sleep efficiency [Phase I ($p<0.001$, $R^2 = 0.991$) Phase II ($p = 0.002$, $R^2=0.998$)] in Parkinson's patients but Clonazepam did not have any significant effect on wake after sleep onset, stage I sleep, sleep latency and wakefulness. Hence a larger population based longitudinal study should be performed to validate these findings.

Key words: Sleep lantency, sleep efficiency, video polysomnography, clonazepam, parkinson's disease

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INTRODUCTION

Parkinson's Disease (PD) is one of the most common neurodegenerative movement disorder characterized by its cardinal motor symptoms of rigidity, bradykinesia, resting tremor and postural instability (Swick, 2012). Estimates of the prevalence of sleep disturbance in PD range from 25 to 98% (Schrag *et al*., 2002). Sleep disturbances, which includes Restless Legs Syndrome (RLS), sleep fragmentation, daytime somnolence, Rapid Eye Movement (REM), sleep-disordered breathing, nightmares and sleep behaviour disorder (RBD) are estimated to occur in 60 to 98% of patients with PD (Tandberg *et al*., 1998; Lees *et al*., 1988; Thorpy, 2004; Friedman and Chou, 2004). Sleep disturbance can occur in the early clinical stages of PD and may even predate the onset of PD. There is conflicting evidence as to whether the degree of sleep disorder correlates with Hoehn and Yahr staging of PD (Porter *et al*., 2008; Goetz *et al*., 2010). The loss of dopamine in the striatum leads to neuronal degeneration of the substantia nigra pars compacta is a major idiosyncratic in the pathology of PD. Preclinical studies have shown that c-amino-butyric acid A ($GABA_A$) -agonists decrease extracellular concentrations of dopamine in the striatum (Paladini *et al*., 1999; Smolders *et al*., 1995). Benzodiazepines are an important class of drugs that stimulate $GABA_A$ (Goodman *et al*., 2005). Patients with PD frequently use benzodiazepines (Van De Vijver *et al*., 1999), for sleep disorders and anxiety are common (Olanow and Koller, 1998). The hypnotic drugs were developed especially for the treatment of sleep disturbances but several drugs produce undesired side effects that affect normal sleep in PD patients. Clonazepam is a highly-potent benzodiazepine with a long half-life. Clonazepam was initially licensed as an anti-epileptic agent, but it is used in a wide variety of psychiatric and neurological conditions (Nardi *et al*., 2013), Although, Clonazepam is perceived as "safe," addiction medicine specialists have found that, it is also frequently abused as a street drug (Roache and Meisch, 1995) and there was no comparative advanced video Polysonmography (PSG) report found in PD patients with sleep disorders among the Indian population before and after the treatment of Clonazepam. So a prospective, pilot comparative study was carried out using video PSG to evaluate the sleep quality in PD patients before and after add-on therapy of Clonazepam.

MATERIALS AND METHODS

Study design and subjects: A total six male subjects including three inpatients of PD with sleep disorders and three controls frequency matched with age (±5 years) recruited for the prospective pilot study. The PD inpatients were shifted from the Neurology ward, SRM Medical College Hospital and Research Centre to the Sleep lab, Metabolic ward during study hours. Controls were healthy volunteers without any chronic or terminal illness recruited from the same geographical locations. Written informed consent was taken from all the study subjects. The study was approved by an institutional ethics committee of SRM Medical College Hospital and Research Centre and the procedures followed were in accordance with the applied guidelines.

The study was conducted in two phases, in first phase all the six subjects (one by one in alternative days) were involved in the overnight polysomnographic study. PD patients without Benzodiazepine reading was monitored and Clonazepam was given as an add on therapy with regular therapy to the PD patients with sleep disorders and polysomnogram was recorded again. After a week of washout period, the second phase was carried out same as that of first phase and sleep pattern was recorded through polysomnography using software Sleep care version 1.01.

Polysomnographic parameters: Overnight polysomnography was conducted using standard techniques and all studies were performed in accordance with guidelines published by the American Academy of Sleep Medicine (AASM). Polysomnography consisted of continuous recordings of central and occipital electroencephalograms, bilateral electrooculograms, submental and bilateral tibial electromyograms and electrocardiogram. Nasal and oral airflow were measured using both thermocouple sensors and Pressure Transducer Airflow (PTAF) monitoring devices. Body positioning was verified by infrared video recording. Studies were scheduled to last between 6 and 8 h and were terminated following the final wakening. Polysomnograms were scored in 30-sec epochs, following criteria of Rechtschaffen and Kales for sleep staging (Rechtschaffen and Kales, 1968). All studies were recorded by a registered polysomnography technician. In addition, all studies were reviewed and interpreted by a neuro specialist from SRM Medical College Hospital and Research. A number of sleep variables were derived from the sleep-stage score data. Total Time In Bed (TIB) was computed as the total time from lights-out to wake-up time. Total Sleep Period (TSP) was defined as the length of time from sleep onset to wake up:

$$TST = TRT\text{-}TWT\text{-}TMT \quad (1)$$

$$\text{Sleep effiency} = \frac{\text{TST}}{\text{TRT}} \times 100 \quad (2)$$

Total Sleep Time (TST) was defined as all sleep time in TIB. Sleep efficiency was computed as the ratio of all sleep time to total time in bed both including and excluding stage I sleep. Stage I, REM and NON-REM sleep was calculated using following formulas. Minutes and percentage of each sleep stage and AMT time were computed in relation to TSP. Minutes of AMT were also calculated by third of TSP. Arousals were defined as the total number of awake episodes of 0.5 min or longer duration in TSP:

$$\text{Stage N1}(\%) = \frac{\text{Total N1[min]}}{\text{TST}} \times 100 \quad (3)$$

$$\text{REM}(\%) = \frac{\text{Total (in min)}}{\text{TST}} \quad (4)$$

$$\text{Non} - \text{REM}(\%) = \frac{\text{N1} + \text{N2} + \text{N3 (in min)}}{\text{TST}} \times 100 \quad (5)$$

Medication: After the beseline Polysomnogram, patients were administered openly Clonazepam (0.25 mg) under the supervision of physician about one hour before bed time and electrodes were fixed according to guidelines, PSG parameters were recorded. Same procedure was applied in the phase II also. Patients activities were monitored over video throughout the night.

Statistical analysis: Continuous variables were analyzed using the Student's t test and categorical variables were compared using a chi-squared analysis. All tests were two-tailed and P values<0.05 were assumed to represent statistical significance. Data are presented as mean±standard deviation. All analyses were performed using the Statistical Package for the Social Sciences 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Description of study participants: Demographics and drug history derived from the screening questionnaires for the subjects are presented in Table 1. Participants age ranged from 48 to 68 healthy volunteers (51.33±3.51 years) and PD patients (60.0±8.00 years). The study subjects were mostly well-educated and married. None of the patients had other major co-morbidities. No participants reported using alcohol or other behavioral interventions to improve sleep.

Table 1: Demographics and drug history

Demographics	Healthy volunteers	PD Patients
Age (years, mean±SD)	51.33±3.51	60.0±8.00
Marital status (n)		
Married	2	3
Single	1	-
Economic status (n)		
Lower	2	1
Middle	1	3
Education (n)		
High school	2	2
Under graduate	2	1
Post graduate	1	1
Occupation (n)		
Service	2	1
Business	1	-
Retired	-	2
Level of activity		
Active	2	-
Routine work	1	2
Drug history		
	-	Levodopa + Carbidopa (125 mg) Trihexyphenidyl hydrochloride (2 mg) Pantoprazole (40 mg) Multivitamin tablets

Values are expressed in mean±SD

Polysomnographic evaluation: To determine the stages of sleep, an electroencephalogram (with four channels, two central and two occipital), chin electromyogram (with one channel) and electro-oculogram (with two channels) were obtained. Baseline PSG sleep characteristics for patients, healthy volunteers and comparison with add-on therapy are presented in Table 2.

Phase I sleep study: Healthy volunteers sleep pattern was compared with PD patients, sleep latency was increased in PD patients compared to healthy volunteers ($p = 0.004$, $R^2 = 0.896$) but no significant effect with Clonazepam as add on therapy among the PD patients ($p = 0.606$, $R^2 = 0.072$). Healthy volunteers Wake After Sleep Onset (WASO) was low when compared to PD patients ($p<0.001$, $R^2 = 1.00$) but no significant difference with add-on therapy amongst PD Patients ($p = 0.524$, $R^2 = 0.065$). PD patients sleep efficiency was considerably less than healthy volunteers ($p = 0.003$, $R^2 = 0.998$) and also Clonazepam significantly increases the sleep efficiency ($p<0.001$, $R^2 = 0.991$) in PD patients.

Phase II sleep study: After a period of a week, the second phase was carried out same like phase I. Sleep latency was compared between healthy volunteers and PD patients. The difference was highly significant ($p<0.001$, $R^2 = 0.999$) but there was no considerable effect of Clonazepam in PD

Table 2: Polysomnographic evaluation of study subjects in two different phases

	Phase I			Phase II		
Sleep parameters	Healthy volunteers	PD Patients (without Clonazepam)	PD Patients (with Clonazepam)	Healthy volunteers	PD Patients (without Clonazepam)	PD Patients (with Clonazepam)
Time in bed (min)	404±38.60	436.0±38.6	444±41.6	470±17.3	398.0±39.9	424±54.1
Total sleep time (min)	350.7±72.8	271.3±82.1	297.3±79.4	384±9.17	284.3±49.2	323±59.5
Sleep latency (min)	13.6±0.52	27.23±3.05**	24.10±3.44	11.1±0.55	31.07±4.07***	27.6±3.08
WASO (min)	33.67±3.21	73.3±20.8**	68.5±18.1	28.0±3.0	83.33±6.93	77.67±9.65
Sleep efficiency (%)	87.4±1.65	64.57±11.2**	72.77±4.46**	90.25±1.55	71.07±5.46***	75.73±4.60
N1	16.93±5.44	125.2±38.1	115.5±10.61	19.93±1.60	138.3±23.0	152.6±26.7
N2	146.5±43.4	3.30±1.12	5.03±1.419	173.83±7.57	0.33±0.231	3.39±2.52
N3	105.1±21.1	0.657±0.44	2.06±1.23	115.60±1.51	0.167±0.289	3.4±0.98
REM	32.47±6.19	4.85±1.35	5.33±2.00	35.76±0.37	2.90±2.17	4.40±2.69
WAKE	32.37±6.37	135.9±42.6	125.9±22.3	36.56±0.58	140.7±23.6	201.4±54.5

Values are expressed in mean±SD, *p<0.05, **p<0.01, ***p<0.001

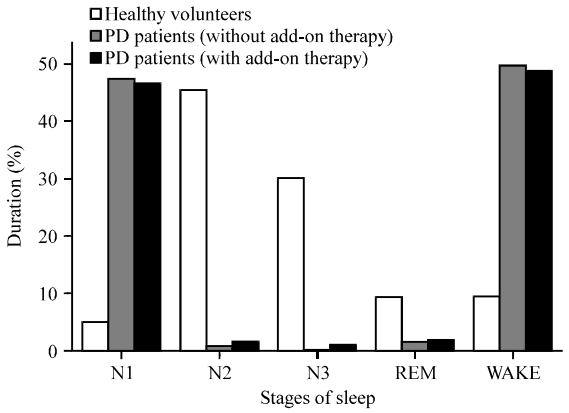

Fig. 1: Comparison of duration of sleep stages among healthy volunteers, PD patients and PD patients with Clonazepam as an add-on therapy

Patients ($p = 0.726$, $R^2 = 0.081$). Duration of WASO was very high in PD patient when compared to healthy volunteers but there was no substantial difference in Clonazepam add-on therapy ($p = 0.826$, $R^2 = 0.072$). Better sleep efficiency was recorded in healthy volunteers ($p = 003$, $R^2 = 0.9994$). Similar like phase I sleep study, the Clonazepam therapy was sound significant ($p = 0.002$, $R^2 = 0.998$) on sleep efficiency in PD patients.

Different stages of sleep and its duration in healthy volunteers, PD patients and PD patients with Clonazepam was comparatively shown in bar graph (Fig. 1). Mean stage I sleep duration of healthy volunteers were relatively less (4.9%) than PD patients with add-on therapy (46.6%) and without add-on therapy (47.4%). Stage II sleep duration of healthy volunteer (45.41%) was quite more than PD patients with (0.68) and without (1.5%) add-on therapy. Stage III duration of sleep also significantly less when compared to healthy volunteers in PD patients with (1.73%) and without add-on therapy (0.15%). REM duration was more in healthy volunteers and wake was more in PD patients, there was no significance in add-on therapy on these parameters. Each stage of sleep is characterized by a level on the vertical axis of the graph with time of night on the horizontal axis. Polysomnogram (Fig. 1-3) showed that the difference of Delta wave and K complexes in healthy volunteers, PD patients with and without Clonazepam add-on therapy (Fig. 4).

DISCUSSION

The present pilot study aimed at evaluation of sleep pattern and duration of different stages of sleep in PD patients before and after add-on therapy of Clonazepam. In this study, PD patients with sleep disorders were recruited and administered Clonazepam openly and the sleep parameters were measured. Sleep-related problems specific to PD may occur early and even predate the diagnosis of the disease but are generally more frequent and more severe in patients with advanced PD. These problems can seriously compromise patients' quality of life and lead to impaired functioning in daily activities (Dhawan *et al*., 2006). The present study was reported the Stage I, II, III and REM sleep of PD patients having highly significant difference with healthy volunteers and this might lead to increase in frequency with advancing disease. A sleep study may show a low total sleep time, many awakenings, a short REM latency and short slow-wave sleep (stages III and IV); the patient experiences the problem as light sleep with frequent awakenings (Pandya *et al*., 2008). The firing rates of the LDT/PPT neurons are sleep state-specific with high-frequency firing during wakefulness with decreased firing during Stages N1-N3 of non-REM sleep (Swick, 2012). Parkinson's disease is associated with increased sleep latency and fractured sleep architecture with increased of Stage I sleep and a reduction of REM Sleep. This dysfunction is multifactorial in origin and related to motor problems of Parkinson's such as stiffness. Nocturia and medication effects of Dopamine Agonists (Das) have been known to increase nocturnal activity and cause

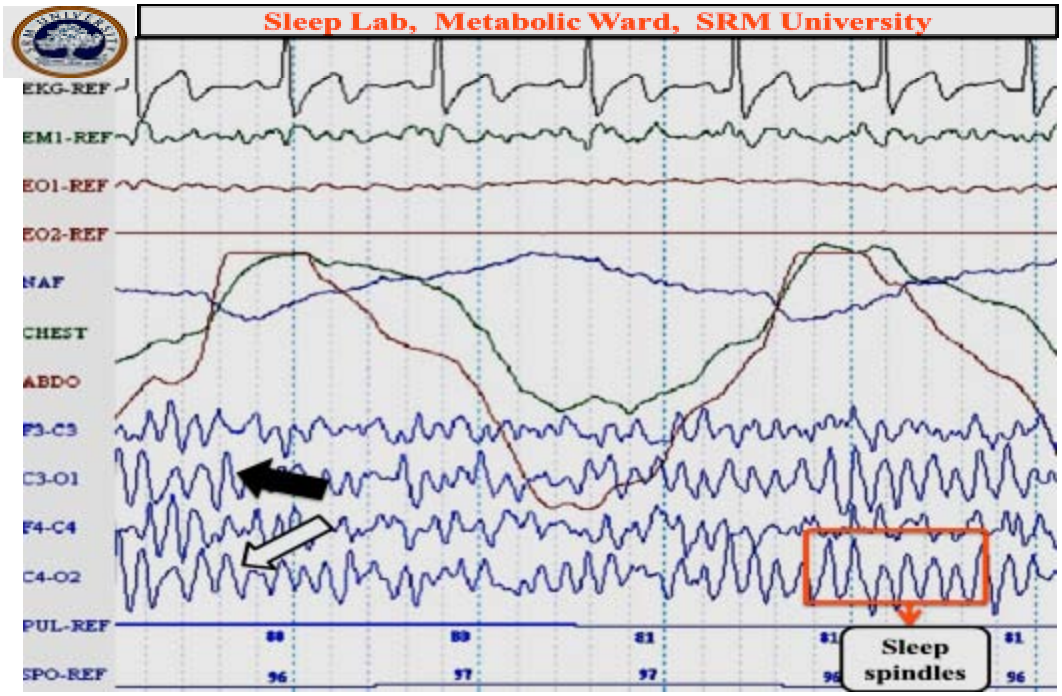

Fig. 2: Delta wave (White arrow), K complexes (Balck arrow) and Sleep spindles in healthy volunteer

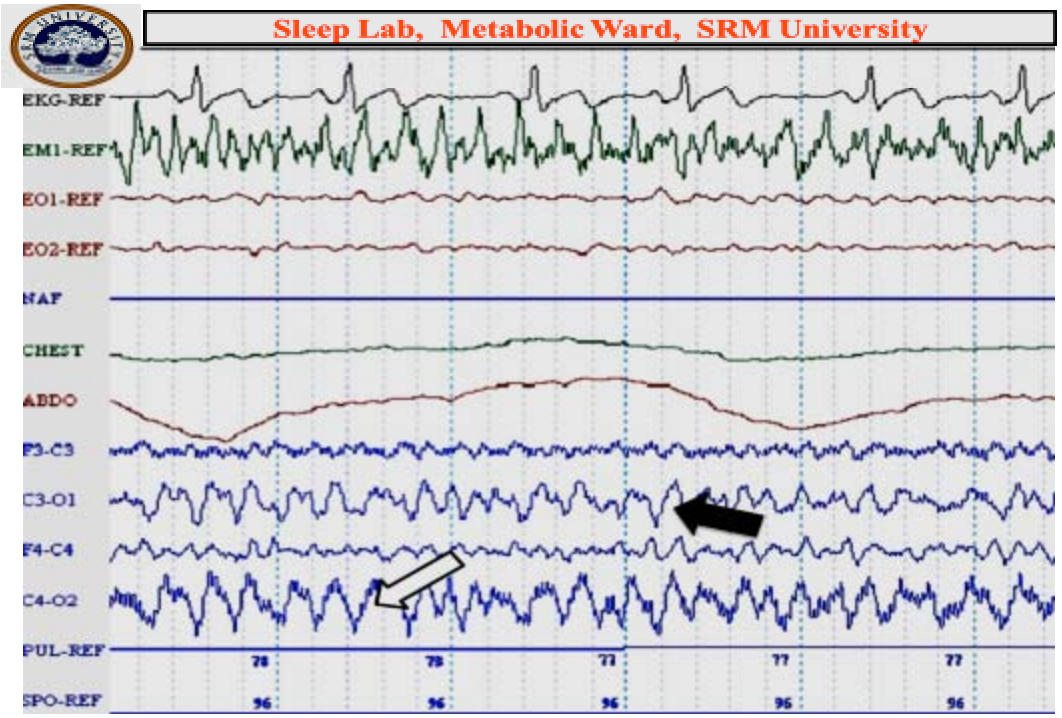

Fig. 3: Delta wave (White arrow), K complexes (Balck arrow) in PD patients with sleep disorders

sleep disruption (Porter *et al*., 2008). The present study was complied with the previous evidence as PD patients had increased sleep latency considerably compared to healthy volunteers.

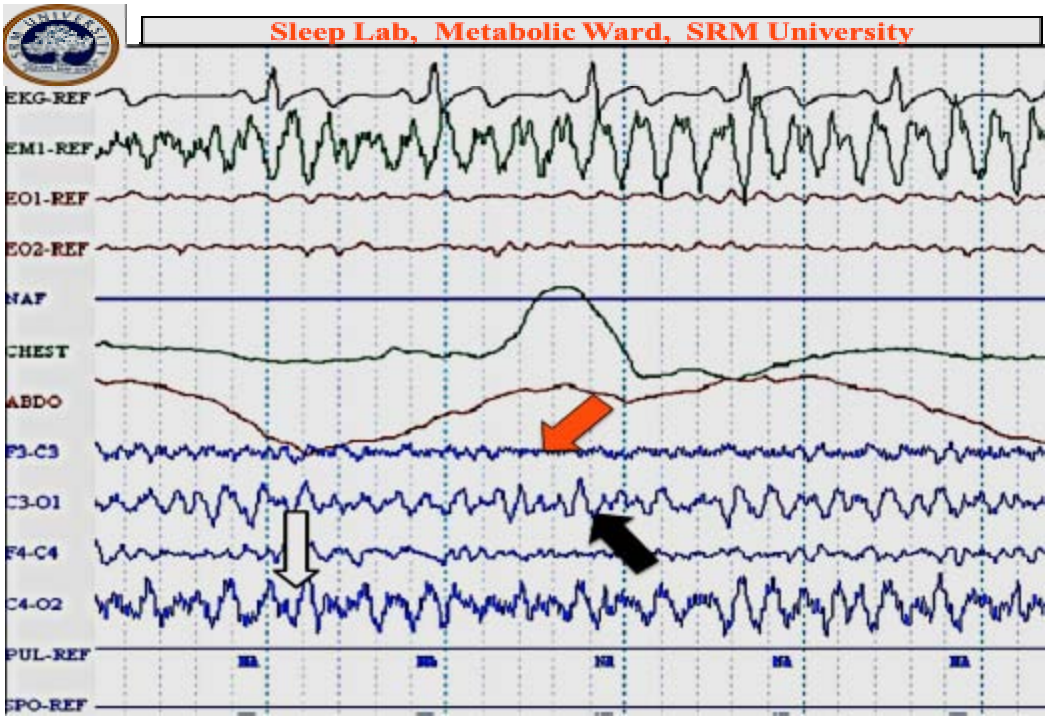

Fig. 4: Delta wave (White arrow), K complexes (Balck arrow) and beta wave (Red arrow) in PD patients with sleep disorders (Clonazepam add-on therapy)

Polysomnographic recordings using Electrooculogram (EOG), Electromyogram (EMG) and Electroencephalogram (EEG) can be used to divide sleep into stages. In some ways, sleep staging is an artificial construct designed for analysis of sleep based on our available monitoring techniques. However, research has revealed that, these sleep stages have physiologic and behavioral correlates that are clinically important. The quantity of K-complexes and sleep spindles in treated Parkinson's disease patients and in the healthy control group were not significantly different between the two groups. This suggested that K-complexes and sleep spindles are not related to the degree of dopaminergic degeneration in treated Parkinson's patients (Happe *et al*., 2004). A substantial number of patients benefited from Clonazepam (54%) as reported previously, but 58% of patients had significant side effects with this medication (Anderson and Shneerson, 2009). We found that a moderate increase in the sleep stages but it does not produce any side effects without drowsiness, which did not reach statistical significance and confirm previous findings in the literature (Iranzo *et al*., 2002). Some potential limitations of the present study must be acknowledged. Even though it was a pilot study, the sample size was rather small. Phase I and Phase II studies were conducted three repeated nights only.

CONCLUSION

Our study suggests that, Clonazepam add on therapy significantly improves the sleep efficiency in both the phases. There was a prolonged WASO, stage I sleep, sleep latency and wakefulness in PD patients but Clonazepam does not have any significant effect on these parameters. A larger population based longitudinal study must be performed to justify these findings.

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