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Fluoxetine for stroke recovery improvement – the double-blind, randomised placebo-controlled FOCUS-Poland trial

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ABSTRACT

Aim of study. The Fluoxetine Or Control Under Supervision (FOCUS)-Poland trial tested in a Polish cohort the hypothesis that fluoxetine improves recovery after stroke.

Clinical rationale for study. Some studies have suggested that fluoxetine may improve functional outcomes after stroke, but these results needed confirmation. Between 2012 and 2014, large clinical trials were initiated by the FOCUS Trial Collaboration. Recently, results from the UK, Sweden, Australia, New Zealand and Vietnam have been published. We here present the results of the FOCUS trial conducted in Poland.

Material and methods. This was a randomised, double-blind, placebo-controlled study based on the FOCUS trial protocol. Patients who had a persisting neurological deficit were randomly assigned 2-15 days after stroke onset to receive for six months either fluoxetine 20 mg/day or a placebo. The primary outcome was functional status measured using the modified Rankin Scale (mRS) at six months after randomisation. Functional status at 12 months was also assessed, as was neurological deficit at six and 12 months. Data was also collected on adverse events.

Results. Between 19 December 2014 and 13 March 2018, 30 patients were given fluoxetine and 31 were given a placebo. For the primary outcome, the distribution across mRS categories was similar for the fluoxetine and placebo groups at six months (common odds ratio 0.88; 95% confidence interval 0.31–2.50; p = 0.81), and there was no difference at 12 months (p = 0.864). There were no differences between groups in stroke recovery or in motor function recovery of the affected hand. There were no significant differences in any other secondary outcomes at six or 12 months. Patients given fluoxetine were less likely than those given the placebo to receive new antidepressant medication within six months (2 [6.67%] vs. 4 [12.90%]).

Conclusions and clinical implications. Consistent with other trials based on the FOCUS protocol, fluoxetine did not improve motor recovery or general stroke outcome at six and 12 months in the Polish cohort studied. However, patients receiving fluoxetine required therapy with additional antidepressant medication less frequently.

Key words: acute stroke, fluoxetine, stroke outcome, motor recovery.

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Introduction

Stroke is the second leading cause of death worldwide and one of the leading causes of disability in adults. Its incidence is constantly increasing, which is mainly due to the ageing of the population [1].

Post-stroke depression is a common sequel that may affect functional outcome [2]. Selective serotonin reuptake inhibitors (SSRIs) have been used for more than three decades to treat mood disorders. However, preclinical studies have shown that the selective SSRI, fluoxetine, can also improve neurobehavioural outcomes by as much as 52%,

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probably by exerting neuroprotective and neuroregenerative effects [3–5].

In 2011, the FLAME (Fluoxetine for Motor Recovery after Acute Ischaemic Stroke) study reported that fluoxetine treatment enhanced motor recovery [6]. In the 113 patients analysed (fluoxetine, n = 57; placebo, n = 56), improvement in Fugl-Meyer motor scale (FMMS) scores at day 90 was significantly greater in the fluoxetine group (adjusted mean 34.0 points [95% CI 29.7-38.4]) than in the placebo group (24.3 points [19.9–28.7]; p = 0.003). The FLAME trial results encouraged further research evaluating the beneficial effect of SSRIs for improving motor recovery and stroke outcome.

A subsequent meta-analysis of eight studies including 1,549 patients found that SSRIs caused a decrease in the National Institutes of Health Stroke Scale (NIHSS) compared to a placebo (p = 0.005) [7]. Early SSRI treatment also significantly improved Barthel score (p = 0.005) and functional independence (p < 0.0001), and demonstrated the additional benefit of reducing neurological deficit in patients undergoing rehabilitation after a stroke. A later Cochrane systematic review of SSRIs for stroke recovery of 63 trials (9,168 patients) found no reliable evidence that SSRIs should be used routinely to improve recovery after stroke; however, this review included relatively small cohorts of patients [8].

Clinical rationale for this study

To provide conclusive and robust evidence regarding the effect of SSRIs for stroke recovery, three large clinical trials with the same core protocol were initiated: FOCUS (Fluoxetine Or Control Under Supervision), AFFINITY (Assessment of Fluoxetine in Stroke Recovery) and EFFECTS (Efficacy of Fluoxetine — a Randomised Controlled Trial in Stroke) [9–11].

The trials recruited patients in different regions and countries, but used a common core protocol adapted to local settings. The results of the FOCUS trial were published in 2019 [9], and of the EFFECTS and AFFINITY trials in 2020 [10, 11]. In all three large trials, fluoxetine treatment did not show a functional benefit in patients after stroke, but some safety concerns were raised, including an increased risk of epileptic seizures, falls, bone fractures and hyponatremia in the fluoxetine group versus the placebo group.

Results using the common protocol have been published from the UK, Sweden, Australia, New Zealand and Vietnam. We here present the results from a Polish cohort that used the FOCUS trial protocol to study the effects of fluoxetine on stroke functional outcomes and to identify any other benefits or harms of post-stroke fluoxetine use.

Material and methods

This was a randomised, double-blind, placebo-controlled study to evaluate the effects of routine 6-month use of fluoxetine 20 mg/day versus placebo in patients with acute stroke based on the FOCUS, AFFINITY and EFFECTS trials protocol [12]. The study was approved by the local Ethics Committee.

All adult patients hospitalised in the 2nd Department of Neurology at the Institute of Psychiatry and Neurology in Warsaw due to ischaemic or haemorrhagic stroke were invited to take part in the trial. The diagnosis of stroke was based on clinical symptoms and brain imaging, usually plain computed tomography (CT) but in some cases magnetic resonance imaging (MRI). Stroke severity was assessed at randomisation with the National Institutes of Health Stroke Scale (NIHSS) [13]. We used the Oxfordshire Community Stroke Project (OCSP) [14] categories, organised by lesion location, and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [15] classification of stroke causes for ischaemic strokes. Additional inclusion criteria were: the ability to randomise the patient 2-15 days from the onset of stroke and the presence of persisting focal neurological deficit at randomisation. The deficit had to be severe enough to justify fluoxetine treatment from the patient's or the caregiver's perspective. All patients signed informed consent.

Exclusion criteria were: subarachnoid haemorrhage (unless secondary to intracerebral bleeding); current or recent depression (up to one month) requiring treatment with SSRIs; current use of drugs that cause significant interactions with fluoxetine: the use of monoamine oxidase inhibitors (MAOi) up to five weeks prior to study enrollment (e.g. phenelzine, isocarboxazide, tranylcypromine, moclobemide, selegiline and rasagiline) or pimozide; high probability that the patient would not be available during follow-up (e.g. another life-threatening illness); being unable to understand spoken or written Polish (e.g. aphasia hindering communication); history of epileptic seizures; history of allergy to fluoxetine; suicide attempt or self-harm; hepatic impairment (ALT > 3 above the upper normal limit) and renal impairment (creatinine > 180 micromol/L).

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either fluoxetine or a placebo, by use of a computer-based permuted block randomisation. Optimum balance between treatment groups was controlled for age (≤ 70 *vs* > 70 years) and NIHSS (≤ 7 *vs* > 7). Clinicians involved in randomisation and outcome assessments, the patients, and their families, were all masked so as to be unaware of treatment allocation. The placebo capsules were visually identical to the fluoxetine capsules, even when broken open.

Procedures

Fluoxetine 20 mg or a placebo was administered orally once daily for six months. The study medication (active and placebo) was manufactured and donated by Polpharma (Poland). Patients received 186 capsules and were recommended to take the study medication once a day (in the morning). Adherence to the study medication was measured by recording the date of the first and last dose taken and the number of

missed doses. Unused capsules were returned. The reasons for stopping the study medication early were recorded.

Those patients who developed post-stroke depression during the study period received a higher dose of fluoxetine (40 mg daily instead of 20 mg) or another SSRI was added to fluoxetine.

Outcome measures

The primary outcome measure was the modified Rankin scale (mRS) [16] at the 6-month follow-up. We also evaluated health status with the Stroke Impact Scale (SIS; for each of nine domains, on which the patient scored between 0 and 100) at six months [17]. Neurological deficit was evaluated with NIHSS at randomisation, then after six and 12 months. The severity of arm and hand neurological deficit was assessed by NIHSS, the Medical Research Council (MRC) scale [18] and the Brunnström scale [19] at the six months follow-up. Each researcher responsible for clinical evaluation received certification in the application of the mRS and NIHSS prior to study initiation. Dependency after six and 12 months was evaluated in the Barthel index (BI, scores 0–20) and mRS [20].

We also evaluated health status with the Stroke Impact Scale (SIS; for each of nine domains, on which the patient scored between 0 and 100) at six months [17]. Mental Health Inventory (MHI-5) was used for mood assessment [21, 22]. Overall rating of recovery was assessed on a visual analogue scale (VAS). EuroQoL-5 Dimensions-5 Levels (EQ5D-5L) was used to measure health-related quality of life [23].

Adverse events and safety outcomes were recorded including recurrent stroke (ischaemic and haemorrhagic), acute coronary syndromes, hyponatremia (< 125 mmol/L), epileptic seizures, upper gastrointestinal and other major bleeding (lower gastrointestinal, extracranial, subdural, extradural, and subarachnoid), hyperglycaemia (> 22 mmol/L) and symptomatic hypoglycaemia, bone fractures, falls causing injury, new depression, new antidepressant prescription, and self-harm.

Statistical analysis

No formal sample size calculation was conducted; funding constraints determined the final number of patients enrolled. An intention-to-treat approach was adopted to compare groups using two-tailed Fisher's exact test, chi-square test, Mann-Whitney test and unpaired Student's t-test, where appropriate. Ordinal regression was used to calculate the common odds ratio (OR), which represents a shift in scores on the mRS between compared groups. The estimates were adjusted based on the six simple variable (SSV) model (i.e. age; whether independent in activities of daily living before the stroke; living alone before the stroke; ability to lift both arms off the bed; ability to walk unassisted; ability to talk and to talk without confusion), on NIHSS results (< 15 and > 15) as well as mRS prior to stroke, delay from stroke onset to randomisation (2–8 days *vs* 9–15 days), motor deficit (present or absent) or aphasia (present or absent).

Results

Between 19 December 2014 and 13 March 2018, 61 patients were recruited. Thirty patients were allocated fluoxetine and 31 were allocated a placebo.

In five cases (fluoxetine n = 3, placebo n = 2; 8.2%), patients or their caregivers withdrew consent and the patients did not complete the 6-month treatment. Two patients died within six months of follow up (one each in the fluoxetine and the placebo group) and one additional patient in the fluoxetine group died within 12 months of study recruitment. In total, 54 (88.5%) patients completed the six months of treatment and took all 186 capsules. The clinical characteristics of the active and placebo groups were well balanced, and are set out in Table 1.

The primary outcome, an ordinal comparison of the distribution of patients across the mRS categories at six months, was similar between the two groups (common OR 0.88; 95% confidence interval 0.31–2.50; p = 0.81; Fig. 1) and there was no difference at 12 months (Tab. 2). In addition, we did not find any differences in the distribution of the BI, NIHSS, MRC or Brunnström scales after six months, or tin he NIHSS and BI after 12 months, between patients allocated fluoxetine and placebo (Tab. 2). There were no significant differences after six months between the fluoxetine and placebo groups in SIS, MHI-5, VAS and EQ5D-5L (Tab. 2).

Patients given fluoxetine less frequently than those given a placebo required an additional dose of fluoxetine or new antidepressant medication due to post-stroke depression within six months (2 [6.67%] versus 4 [12.90%] patients). Patients taking fluoxetine less frequently had a new stroke (2 [6.67%] versus 3 [9.68%]) and were also less frequently hospitalised for any reason (4 [13.33%] versus 7 [22.58%]). In addition, there were no differences in any other events at six or 12 months. Other adverse events in the fluoxetine group included bone fracture (n = 1) and hospitalisation due to severe diarrhoea (n = 1). Adverse events in the placebo group included: epileptic seizure (n = 1), cardiac stimulator implantation (n = 1), constipation (n = 1), diarrhoea (n = 1), and severe nausea (n = 1).

Discussion

Our findings in a Polish cohort add to data from other trials based on the FOCUS protocol (FOCUS, AFFINITY and EFFECTS) [9–11] and confirm that daily administration of fluoxetine 20 mg for six months does not improve functional or general stroke outcome after six and 12 months.

Before FOCUS, previous studies had inconsistently shown positive effects of fluoxetine on some stroke recovery outcomes, such as FMMS scores improvement at day 90 in the FLAME trial [6], and post-stroke neurological deficit in NIHSS, promoted BI and functional independence in a meta-analysis [7].

However, the latest Cochrane systematic review did not find reliable evidence that SSRIs should be used routinely to

Table 1. Baseline characteristics

	Fluoxetine (n = 30)	Placebo (n = 31)	p value
Women	8 (26.7)	13 (41.9)	0.324
Age, [years]	66.60 (12.60)	66.35 (12.46)	0.939
Predicted 6-month outcome based on SSV	0.18 (0.04–0.31)	0.15 (0.02–0.27)	0.391
SSV ≤ 15	12 (40.0)	17 (54.8)	0.366
SSV > 15	18 (60.0)	14 (45.2)	0.366
mRS prior to stroke			0.366
0	20 (66.7)	19 (61.3)	
1	10 (33.3)	10 (32.3)	
2	0 (0.0)	2 (6.5)	
Previous medical history			
Depression history	0 (0.0)	1 (3.2)	1.000
Diabetes	6 (20.0)	9 (29.0)	0.602
Atrial fibrillation	7 (23.3)	5 (16.1)	0.700
Coronary heart disease	5 (16.7)	6 (19.4)	1.000
Hypertension	19 (63.3)	17 (54.8)	0.679
Current smoking	20 (66.7)	22 (71.0)	0.583
Alcohol overuse	6 (20.0)	7 (22.6)	1.000
Obesity	3 (10.0)	2 (6.5)	0.969
Hypercholesterolemia	6 (20.0)	5 (16.1)	0.952
TIA or stroke	5 (16.7)	4 (12.9)	0.958
ICH	1 (3.3)	2 (6.5)	1.000
History of bone fractures	1 (3.3)	5 (16.1)	0.212
Neurological deficits			
NIHSS total score	5.00 (3.25–8.00)	6.00 (4.00–8.00)	0.783
Barthel index	14.50 (9.50–19.75)	12.00 (7.50–18.00)	0.420
Arm MRC scale			0.099
0	7 (23.3)	7 (22.6)	
1	0 (0.0)	2 (6.5)	
2	0 (0.0)	2 (6.5)	
3	2 (6.7)	4 (12.9)	
4	18 (60.0)	9 (29.0)	
5	3 (10.0)	7 (22.6)	
Arm Brunnström scale			0.899
1	7 (23.3)	8 (25.8)	
2	1 (3.3)	2 (6.5)	
3	1 (3.3)	2 (6.5)	
4	4 (13.3)	3 (9.7)	
5	12 (40.0)	9 (29.0)	
6	5 (16.7)	7 (22.6)	
Predictive variables			
Able to lift both arms	22 (73.3)	18 (58.1)	0.324
Able to walk at randomisation	20 (66.7)	15 (48.4)	0.236
Current mood, PHQ 2			0.478

Table 1 cont. Baseline characteristics

	Fluoxetine (n = 30)	Placebo (n = 31)	p value
0 yes responses	27 (90.0)	30 (96.8)	
1 yes responses	2 (6.7)	1 (3.2)	
2 yes responses	1 (3.3)	0 (0.0)	
ICH	3 (10.0)	4 (12.9)	1.000
Secondary ICH	3 (10.0)	3 (9.7)	1.000
OCSP classification of ischaemic stroke			0.564
Total anterior circulation infarct	12 (40.0)	12 (38.7)	
Partial anterior circulation infarct	7 (23.3)	11 (35.5)	
Lacunar infarct	2 (6.7)	0 (0.0)	
Posterior circulation infarct	6 (20.0)	5 (16.1)	
Cause of stroke according to TOAST classification			0.839
Large artery disease	10 (37.0)	9 (32.1)	
Small vessel disease	4 (14.8)	3 (10.7)	
Embolism from the heart	6 (22.2)	6 (21.4)	
Another cause	0 (0.0)	1 (3.6)	
Unknown or uncertain cause	7 (25.9)	9 (32.1)	
Drug taken at hospital discharge	29 (96.7)	31 (100.0)	0.987
Discharge to			0.496
Own home	19 (63.3)	18 (58.1)	
Rehabilitation ward	10 (33.3)	13 (41.9)	

Data presented as n (%), mean (standard deviation), or median (interquartile range).
SSV — six simple variable; TIA — transient ischaemic attack; ICH — intracranial haemorrhage; NIHSS — National Institutes of Health Stroke Scale; MRC — Medical Research Council (0 – no contraction, 5 – normal power); PHQ-2 — Patient Health Questionnaire-2; OCSP — Oxfordshire Community Stroke Project; TOAST — Trial of Org 10172 in Acute Stroke Treatment

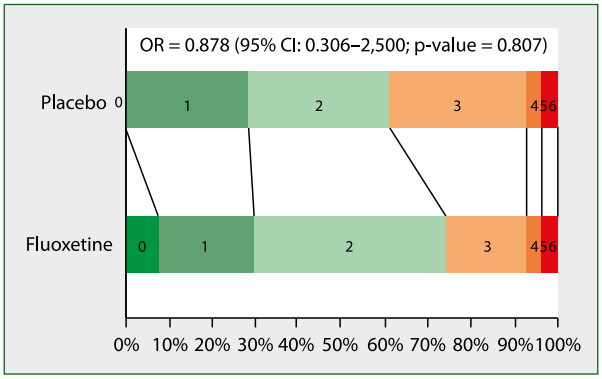

Figure 1. Primary outcome of disability on modified Rankin Scale (mRS) at six months by treatment group. Ordinal analysis of mRS adjusted for the six simple model results, mRS prior to stroke, delay from stroke onset to randomisation, motor deficit, and aphasia

improve recovery after stroke [8]. We also did not confirm a positive effect of fluoxetine on general outcome (mRS and BI), neurological deficit reduction (NIHSS), or improvement of hand motor function (NIHSS, MRC and Brunnström scale). We used different scales for upper extremity motor function assessment than the FLAME trial. Both our study and FLAME were conducted on relatively small cohorts, which may also have contributed to the differing results.

In vitro, in vivo and clinical studies suggest that SSRIs have a negative effect on bone density and the risk of fracture at the therapeutic dose levels widely used for the treatment of depression in current clinical practice [24]. In our study, one female receiving fluoxetine had a bone fracture, compared to no fractures in the placebo group. This is consistent with previous trials which also reported more frequent bone fractures in patients taking SSRIs [9–11, 25] and confirms the findings from observational studies [26].

Two patients taking fluoxetine in our cohort required an additional dose of fluoxetine or a new antidepressant medication, compared to four in the placebo group. This is consistent with large trials evaluating the benefit of six months of fluoxetine administration, which have also reported that patients given fluoxetine were less likely than those given a placebo to have developed new depression at six months [9–11].

Some studies have suggested that enhanced serotoninergic transmission (probably caused by inhibition of serotonin reuptake with fluoxetine) may be associated with a small decrease in the rate of ischaemic stroke [27]. However, we did not observe this trend in our study (one patient in each group), which is consistent with results from the FOCUS, AFFINITY

Table 2. Secondary outcome measures for stroke recovery after six and 12 months in fluoxetine and placebo groups

Outcome	Fluoxetine (n = 30)	Placebo (n = 31)	p value
Stroke recovery after 6 months			
Barthel index	20.00 (19.00–20.00)	20.00 (18.50–20.00)	0.688
NIHSS, total score	2.00 (1.00–3.00)	1.00 (1.00–3.50)	0.891
NIHSS, affected arm			0.584
0	20 (66.7)	18 (58.1)	
1	1 (3.3)	4 (12.9)	
2	0 (0.0)	2 (6.5)	
3	3 (10.0)	2 (6.5)	
4	2 (6.7)	1 (3.2)	
NIHSS, aphasia			0.813
0	24 (88.9)	25 (86.2)	
1	2 (7.4)	2 (6.9)	
MRC, affected hand			0.776
0	2 (6.7)	0 (0.0)	
1	2 (6.7)	3 (9.7)	
2	0 (0.0)	1 (3.2)	
3	1 (3.3)	2 (6.5)	
4	8 (26.7)	7 (22.6)	
5	13 (43.3)	14 (45.2)	
Brunnström scale, affected hand			0.891
1	2 (6.7)	1 (3.2)	
2	2 (6.7)	1 (3.2)	
3	1 (3.3)	3 (9.7)	
4	1 (3.3)	1 (3.2)	
5	6 (20.0)	9 (29.0)	
6	14 (46.7)	12 (38.7)	
SIS			
Strength	21.88 (1.56, 40.62)	25.00 (0.00, 50.00)	0.663
Memory	89.29 (82.14, 99.11)	92.86 (82.14, 100.00)	0.397
Emotion	68.06 (58.33, 77.08)	77.78 (58.33, 88.89)	0.378
Communication	98.21 (83.04, 100.00)	100.00 (94.64, 100.00)	0.369
Daily activities	86.25 (66.88, 99.38)	82.50 (58.75, 97.50)	0.496
Mobility	84.72 (72.92, 88.89)	86.11 (61.11, 94.44)	0.617
Manual dexterity	84.38 (29.69, 93.75)	81.25 (18.75, 100.00)	0.957
Participation	90.62 (47.66, 96.88)	53.12 (43.75, 93.75)	0.182
Motor	62.04 (47.69, 64.64)	57.18 (46.30, 66.09)	0.915
Physical	68.78 (49.50, 72.22)	66.11 (46.56, 73.65)	0.880
Vitality	50.00 (39.06, 56.25)	50.00 (43.75, 56.25)	0.993
MHI-5	66.00 (53.00, 72.00)	68.00 (56.00, 78.00)	0.343
VAS	60.00 (50.00, 78.75)	50.00 (40.00, 72.50)	0.374
EQ5D-5L	0.91 (0.83, 0.97)	0.91 (0.83, 0.99)	0.915
Stroke recovery after 12 months			

Table 2 cont. Secondary outcome measures for stroke recovery after six and 12 months in fluoxetine and placebo groups

Outcome	Fluoxetine (n = 30)	Placebo (n = 31)	p value
mRS			0.864
0	1 (3.3)	1 (3.2)	
1	8 (26.7)	9 (29.0)	
2	11 (36.7)	9 (29.0)	
3	4 (13.3)	7 (22.6)	
4	0 (0.0)	1 (3.2)	
Barthel index	20.00 (19.75–20.00)	20.00 (18.50–20.00)	0.622
NIHSS, total	1.00 (1.00–2.25)	2.00 (1.00–3.00)	0.587
NIHSS, affected arm			0.588
0	20 (66.7)	20 (64.5)	
1	0 (0.0)	3 (9.7)	
2	1 (3.3)	1 (3.2)	
3	2 (6.7)	3 (9.7)	
4	1 (3.3)	0 (0.0)	
NIHSS, aphasia			0.641
0	20 (66.7)	25 (80.6)	
1	4 (13.3)	2 (6.5)	

Data presented as n (%) or median (interquartile range).
NIHSS — National Institutes of Health Stroke Scale; mRS — modified Rankin scale; MRC — Medical Research Council; SIS — Stroke Impact Scale; MHI-5 — Mental Health Inventory 5; VAS — visual analogue scale; EQ5D-5L — EuroQoL-5 Dimensions-5 Levels (where 1 = perfect health and < 0 = worse than death). Presented data only available for those who survived and completed patient questionnaire. The number of patients with missing scores was similar in the two treatment groups

and EFFECTS trials [9–11]. Moreover, there are suggestions that SSRIs may slightly increase the risk of intracranial haemorrhage [28]. This was not reported in our study, a finding consistent with the lack of an increase in intracranial haemorrhage in the FOCUS, AFFINITY and EFFECTS trials [9–11].

Our main study limitation was that this was a small cohort of patients recruited from a single centre in Poland. However, our findings are consistent with those of larger trials using a common protocol, suggesting that this limitation did not substantially impact upon the results. The proportion of our patients who completed 6-month follow-up visits was high (88.5%) and acceptable.

Conclusions and clinical implications

Our results add to a growing and consistent body of evidence that does not support the routine use of fluoxetine within six months post-stroke to promote motor recovery and general outcome after stroke.

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