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RESEARCH ARTICLE

Characteristic of drug-related problems and pharmacists' interventions in a stroke unit in Thailand

Kannikar Semcharoen[1] · Sajja Supornpun[1] · Surakit Nathisuwan[2] · Junporn Kongwatcharapong[1]

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Abstract

Background Little information is available regarding pharmacist's intervention to solve drug-related problems (DRPs) in a stroke unit. *Objective* To investigate the nature and frequency of DRPs along with the role of pharmacists in a stroke unit. *Setting* The study was conducted at the stroke unit of Siriraj hospital, a university affiliated tertiary care hospital in Thailand. *Method* A retrospective descriptive study of DRPs and pharmacists' interventions for stroke patients was performed during July 2015 to December 2016. Data were collected from patient's medical records and pharmacist's intervention record forms. DRPs were categorized using the Hepler–Strand classification. The stroke pharmacist team, consisting of a board-certified pharmacotherapy specialist, neurology pharmacy residents and stroke unit pharmacists, participated in the multidisciplinary ward round in the stroke unit 5 days a week. All patients were visited by a member of the stroke pharmacist team within the first two days of their admission to conduct a thorough review of drug therapy for every patient and provided appropriate recommendation to the multidisciplinary team either verbally during the ward round or with written information in the patients' medical charts, as appropriate. *Main Outcome Measure* (a) incidence and characteristics of DRPs (b) types and the acceptance of pharmacists' interventions. *Results* A total of 859 patients were admitted, of those, 768 patients had ≥ 1 DRPs and a total of 796 DRPs were identified. Clinical pharmacists provided 659 interventions to the multidisciplinary team. The most common DRPs identified were "untreated indications" (22.6%) and "non-compliance" (21.0%). Of all DRPs, 74.6% were stroke related issues. The most implicated drugs were antihypertensive drugs, followed by antithrombotic therapies. The multidisciplinary team accepted 84.7% of pharmacists' interventions. *Conclusion* DRP in a stroke unit is common. Clinical pharmacists in a stroke unit can effectively reduce and prevent DRPs with the focus on performing medication reconciliation, providing recommendation on dosage adjustment and proper drug selection for stroke patients.

Keywords Drug-related problems · Hospital · Pharmacist · Pharmacist's intervention · Stroke · Thailand

Impacts on practice

- DRPs in a stroke unit are common and frequently include the failure to restart the medications for underlying diseases after acute stroke treatment, the use of an inappropriate dose and improper drug selection for patient's condition.
- Clinical pharmacists in a stroke unit should focus especially on performing medication reconciliation, providing recommendation on dosage adjustment and proper drug selection for stroke patients.

Introduction

Ensuring patients' safety has always been an important component of care in any healthcare settings. Drug-related problems (DRPs) have been identified as one of the common causes of morbidity and mortality which also lead to unnecessary spending on healthcare cost [1–4]. Hepler and Strand classified DRPs into eight categories; including untreated indications, subtherapeutic dosage, excessive dosage, drug use without a clear indication, failure to receive drugs,

✉ Junporn Kongwatcharapong
jkwatcharapong@gmail.com

[1] Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand

[2] Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

improper drug selection, drug interactions, and adverse drug reactions [5]. Studies have shown that clinical pharmacists can effectively identify, prevent and resolve clinically significant drug-related problems [6–10]. In terms of practice model, a proactive approach with pharmacists' participation in ward rounds as part of a multidisciplinary team may offer a unique advantage. In this model, pharmacists can directly and effectively prevent or solve DRP at the time of their occurrences.

Patients with stroke may be at an increased risk of DRPs. This is partly a result of advanced age, high prevalence of comorbidities, severity of the disease, and the use of multiple medications, many of which are high risk drugs including medications used in stroke prevention [11]. Previous studies found that there was an average of 1.54–2.01 DRPs per patient admitted with an acute stroke [12, 13]. There were a few studies addressing the role of pharmacists in the identification and resolution of DRPs in stroke setting [12–14]. However, most studies involved a small number of participants and it is unclear whether the pharmacists acted as a part of the multidisciplinary team in a stroke unit.

The Pharmacy Department of Siriraj Hospital has started staffing of clinical pharmacists in the hospital's stroke unit as a member of the multidisciplinary team since 2015. These stroke unit pharmacists have performed both distributive and clinical function to support such service with the focus on identification, prevention and resolution of DRPs to improve patient outcomes. Information regarding patients along with pharmacist's interventions were comprehensively documented. Since a stroke unit has been endorsed by international clinical practice guidelines around the world [15], an evaluation of pharmacist's contribution in such setting would be of value to support pharmacist's role in a stroke unit team. In addition, the availability of this information can be used to support the justification of pharmacist's presence in a stroke unit team in Thailand and other developing countries with similar healthcare context in the Southeast Asian region.

The stroke pharmacist team at Siriraj hospital consisted of a senior clinical pharmacist who is a board-certified pharmacotherapy specialist, neurology pharmacy residents and stroke unit pharmacists. The senior clinical pharmacist was responsible for supervising and providing consultancy to pharmacy residents and the stroke ward pharmacists. At least one pharmacist from the stroke pharmacist team participated in the multidisciplinary ward round in the stroke unit 5 days a week. All patients were visited by a member of the stroke pharmacist team within the first 2 days of their admission. The responsibilities of the stroke pharmacist included reviewing patients' profiles, assisting with medication reconciliation, adjusting doses based on the disease state or renal function, detecting and preventing adverse drug events, monitoring drug interactions, converting intravenous to oral dosage forms, and providing discharge counseling. All necessary information of the patients was obtained from medical charts and patient interview. Any DRPs detected were documented while the plans to resolve them were designed before commencing a ward round. Subsequently, the pharmacist provided recommendations to the multidisciplinary team either verbally during the ward round or with written information in the patients' medical charts, as appropriate. The status of pharmacist interventions was documented as either "accepted" or "not accepted", according to the responses of the attending physicians. Pharmacists performed such activity on a daily basis during Monday–Friday to all patients throughout their hospital stay starting from admission to discharge.

Aim of the study

The aim of this study was to assess the incidence and characteristics of DRPs, types of pharmacists' interventions along with the acceptance rate of such interventions by the multidisciplinary team.

Ethics approval

This study protocol was approved by the Institutional Review Board of Siriraj Hospital. (IRB Number: Si038/2018). Since this study was merely a retrospective review of the routine service that was put in place and data were gathered from existing documents based on routine work. Therefore, a formal consent by an individual patient was not required.

Methods

A retrospective descriptive study was performed during July 2015–December 2016 among stroke patients admitted into the 17-bed stroke unit at Siriraj Hospital, a 2500 bed, university-affiliated tertiary care hospital in Thailand. The sample size was determined to be > 334 patients [14, 16].

For data analysis of our study, patients' clinical characteristics were collected from medical records while characteristics of DRPs, types and the acceptance of pharmacists' interventions were obtained from pharmacists' intervention form. DRPs were categorized according to Hepler–Strand classification [5]. Data on DRPs, drug groups related to DRPs, pharmacist's interventions, and physicians' acceptance rate were analyzed with SPSS software version 18.0 and expressed as percentages.

Results

During the 18-month study period, a total of 859 patients were admitted to the stroke unit. Mean age of the study patients was 66.8 ± 14.6 years and 55.3% were female. For types of stroke, 91.4%, 5.5% and 3.1% of patients experienced ischemic stroke, TIA and hemorrhagic stroke, respectively. The most common comorbidities were hypertension (70.1%), dyslipidemia (43.7%), diabetes (34.0%) and atrial fibrillation (13.7%). About one quarter of the patients previously suffered either a TIA or stroke prior to their admissions. Detail of patient's baseline characteristics are summarized in Table 1.

Among 859 patients included in the study, 768 had one or more DRPs. A total of 796 DRPs were identified, giving an average of 1.04 DRPs per patient. The most common DRP was untreated indications, accounting for 22.6% of the total DRPs. The most common reasons for this DRP were failure to restart the medications for underlying diseases after their discontinuation during the acute treatment phase. Failure to receive drugs due to non-compliance was the second most common DRPs (21.0%) in our study. Although this DRP occurred prior to the hospital admission and did not occur while the patient was in the stroke unit, it was captured during the hospital admission through patient interview. The majority of these cases were non-compliance with medications treating underlying diseases which placed patients at risk of stroke such as anti-hypertensive agents, anti-diabetic drugs and lipid lowering agents. In addition, a notable proportion of patients with a past medical history of stroke, who were prescribed antithrombotic therapies, failed to adhere to such therapy due to the lack of understanding on the importance of those medications. Supra-therapeutic dosage was the third most common DRPs (11.2%) among the study population. The majority of these cases were international normalized ratio (INR) higher than therapeutic level because of inappropriate dosing of warfarin and failure to adjust the dose of medication such as meropenem, piperacillin/tazobactam according to patient's renal function. The different types of DRPs observed in our study are listed at Table 2.

In total, pharmacists provided 659 interventions in response to DRPs. The most common intervention was addition of drugs (34.9%) for a new condition and/or pre-existing conditions of the patients. The latter was most commonly a result of failure to re-order the medications which was discontinued during the acute phase. The second most common intervention was dosage change (22.0%) especially on warfarin to meet the target level and adjustment of antibiotics based on patient's renal function. The third most common intervention was dosage form change or a change in the route of administration (16.7%) when patients were placed on enteral tube feeding. The fourth most common intervention was cessation of a drug (13.2%) that is no longer indicated. Detail information of pharmacists' interventions is presented in Table 3.

For the acceptance rate, 84.7% of pharmacists' interventions were fully accepted which led to changes in therapy. There were 10% and 5.3% of interventions that were partially accepted and not accepted, respectively. Detail of the acceptance rate is presented in Table 4. For drug associated with DRPs, the most common classes of drugs with DRPs were antihypertensive agents (24.6%), antithrombotic agents (20.0%) and statins (14.6%). Detail description of drugs associated with DRPs is shown in Table 5. An example of the impact of pharmacist's interventions was a high rate (75%) of reaching the targeted international normalized ratio (INR) among patients receiving warfarin at the first follow-up visit at an out-patient setting.

Table 1 Demographic details of patients with stroke

Characteristics	Number (%) (n = 859)
Gender	
Female	475 (55.3)
Male	384 (44.7)
Age	
≥ 60	587 (68.3)
< 60	272 (31.7)
Comorbidities	
Hypertension	602 (70.1)
Dyslipidemia	375 (43.7)
Diabetes	292 (34.0)
Previous stroke	230 (26.8)
Atrial fibrillation	118 (13.7)
Type of stroke	
Ischemic stroke	785 (91.4)
Transient ischemic attack	47 (5.5)
Hemorrhagic stroke	27 (3.1)

Discussion

We found that DRPs were extremely common among stroke patients, since 89.4% of stroke patients had at least one DRP. The average incidence of 1.04 DRPs per patient is in line with the findings of other studies. Kanagala et al. [12] reported a rate of 2.015 DRPs per patient in a study of 133 stroke patients who had been admitted to a general medicine ward. Moreover, Celin et al. [13] reported an average of 1.54 DRPs per patient among inpatients admitted with an ischemic stroke to general medicine and neurology wards. There are several explanations on why the average DRP in this study is lower than other studies. First, our study was

Table 2 Type of drug-related problems

Drug-related problems	Number (%) (n = 796)	Example
Untreated indications	**180 (22.6)**	
Re-initiation of therapy for pre-existing conditions		Glipizide, metformin, levothyroxine, allopurinol, colchicine
Addition of drug therapy for prevention or treatment of new condition		Carvedilol, amlodipine, omeprazole
Failure to receive drugs	**167 (21.0)**	
Loss to follow-up		Aspirin, atorvastatin, losartan
Self-discontinuation due to lack of understanding on the importance of secondary prevention drugs		Aspirin, clopidogrel
Supratherapeutic dosage	**89 (11.2)**	
Failure to reduce dosage of antibiotics in renal insufficiency		Piperacillin/tazobactam, meropenem, levofloxacin
Inappropriately high dosage based on patient's condition		Warfarin
Subtherapeutic dosage	**86 (10.8)**	
Failure to increase dosage of antibiotics after acute kidney injury subsided		Vancomycin, amoxicillin/clavulanic acid
Inappropriately low dosage based on patient's condition		Warfarin, nicardipine, labetalol
Improper drug selection	**85 (10.7)**	
Selection of agents to match patient's condition		Candesartan, losartan, carvedilol, bisoprolol
Selection of dosage form in patients requiring nasogastric tube feeding		Aspirin plus dipyridamole ER, theophylline SR, alfuzosin, tamsulosin
Inappropriate diluents for reconstitution or dilution		Phenytoin, amiodarone, fosfomycin, ertapenem
Drug interactions	**79 (9.9)**	Warfarin–phenytoin
		Warfarin–carbamazepine
		Warfarin–prednisolone
		Warfarin–co-trimoxazole
		Warfarin–amiodarone
		Meropenem–sodium valproate
		Clopidogrel–omeprazole
Adverse drug reactions	**61 (7.7)**	
Hepatotoxic, myopathy		Atorvastatin
Headache, palpitation, tachycardia		Aspirin plus dipyridamole, cilostazol
Phlebitis		Nicardipine
Upper gastrointestional bleeding		Warfarin
Hypotension		Hydralazine, carvedilol
Re-exposure to known allergen		Ceftriaxone (in patients with known penicillin allergy)
Drug use without indications	**49 (6.2)**	Metoclopramide, loratadine, acetylcysteine
Prescribing errors	**2 (0.3)**	
Duplication of therapy		Duplicate order for two alpha-blockers (doxazosin, prazosin)
Dosing error		Warfarin dose from 17 mg/week to 21 mg/week

conducted in a stroke unit, which is a specialized service, while other studies were conducted in general wards. The expertise and care level may differ significantly between specialized and general wards. Another possible explanation was the differences in the definition of DRP used across these studies. The Pharmaceutical Care Network Europe (PCNE) system used in other studies is different from the Hepler–Strand classification system used in the current study [5, 17]. The PCNE consists of three groups of primary domains including problems, causes and interventions. Each domain also contains sub-domains. Therefore, PCNE is a much more detail classification system than Hepler-Strand and may lead to more DRPs being identified and counted.

In our study, untreated indications (22.6%) were the most common drug-related problem. DRPs occurred when patients did not receive the medications recommended in standard treatment guidelines for the treatment of their existing diseases or conditions. DRPs also occurred when a prophylactic therapy was not given to the patient who are at risk of developing a new condition. For example, the use of

Table 3 Suggestions provided by intervening pharmacists

Suggestions provided	Number (%) (n = 659)	Example
Addition of drug	230 (34.9)	1. Addition of omeprazole in patients receiving dual antiplatelet who were at high risk of bleeding (HAS-BLED score ≥ 3)
		2. Re-initiation of alpha-blockers for benign prostate hyperplasia after clinically stable
Change in drug dose	145 (22.0)	1. Reduction of piperacillin/tazobactam from 4.5 g IV q 6 h to 2.25 g IV q 6 h in patients with creatinine clearance of < 20 ml/min
		2. Switch from atorvastatin 20–40 mg for better reduction of low-density-lipoprotein cholesterol
Change in route of administration/dosage form	110 (16.7)	1. Switch from phenytoin sustained release to immediate release in patients with nasogastric tube
		2. Switching omeprazole from intravenous to oral route in patients with functioning gastrointestinal tract
Cessation of drug	87 (13.2)	1. Discontinuation of antibiotics where there were unclear signs of infection
		2. Discontinuation of enoxaparin prior to undergoing cardiac catherization
Monitor	51 (7.7)	1. Suggestions to measure vancomycin level
		2. Suggestions appropriate timing to measure international normalized ratio (INR) in patients receiving warfarin
Substitution of drug	36 (5.5)	1. Substitution of warfarin by a new oral anticoagulant in patients with history of labile INR despite long history of warfarin usage
		2. Substitution of enalapril by candesartan for better blood pressure control

Table 4 Results of clinical pharmacists' recommendations

Recommendations	Result (%) (n = 659)
Accepted; change in drug therapy	558 (84.7)
Accepted; no change in drug therapy	66 (10.0)
Not accepted	35 (5.3)

proton-pump inhibitors as a prophylaxis for gastrointestinal bleeding in a patient receiving antithrombotic therapy who is at high risk of bleeding (HAS-BLED score ≥ 3) [18]. In addition, DRPs often stemmed from physicians discontinuing existing medications (e.g., antidiabetic drugs, antihypertensive drugs, thyroid drugs, antigout agents) at admission for patients' underlying diseases during the acute phase of stroke. However, when the clinical status was more stable, those medications were not recommenced even at discharge. In our study, the clinical pharmacists routinely performed a thorough medication reconciliation to compare the medications on admission, during transfer or at discharge. This process effectively helped identify the problem of untreated indications. When a DRP was found, the pharmacist suggested to the responsible physician to add the appropriate drugs to resolve the problem.

During the conduct of our study, we found that about 1 in 5 of patients were non-compliant to important drugs such as antiplatelets or antihypertensive drugs before their admissions. Lack of awareness on the importance of those medications along with financial barriers were identified. While we acknowledged that this DRP occurred outside of a stroke unit, we believe it is crucial to report this very important DRP. By addressing it, we may increase awareness of a pharmacist working in a stroke unit to perform a thorough patient interview and patient education to solve this issue. Identifying the reasons behind patients' non-compliance is an important step in resolving it. As a result, an effort must be made to identify the root cause of non-compliance so that an appropriate intervention can then be tailored to assist the patient.

Dosage adjustment was a common intervention performed by pharmacists in our study. A number of stroke patients required warfarin therapy. Clinical pharmacists can assist the multidisciplinary team in managing warfarin based on a thorough understanding on the complex pharmacokinetics and pharmacodynamics properties of the drug. In addition, most stroke patients are elderly patients with poor renal function. Using clinical pharmacists to monitor and adjust medication based on renal function can be of benefit to the multidisciplinary team to reduce cost of excess use of medications along with avoidance of toxicity from drug accumulation.

Improper drug selection was quite common in a stroke unit. Interestingly, inappropriate selection of dosage form may be a common and unique issue in a stroke unit. An example of this issue was the prescribing of a combination product of aspirin and modified release dipyridamole through enteral tube feeding. This product when crushed may alter the release profile of dipyridamole which may affect its effectiveness. Since a significant proportion of stroke patients may require enteral tube feeding, use of modified-release drug products can be problematic. This

Table 5 Drugs featured in the 796 drug-related problems

Drugs group	Number (%) (n = 796)
Antihypertensive drugs	**196 (24.6)**
Beta-blockers	
Carvedilol	27
Bisoprolol	22
Metoprolol	15
Propranolol	4
Atenolol	3
Angiotensin-converting enzyme inhibitors (ACEIs)	
Enalapril	46
Angiotensin II receptor blockers (ARBs)	
Losartan	15
Calcium channel blockers (CCBs)	
Amlodipine	31
Manidipine	12
Nicardipine	7
Others	
Doxazosin	8
Hydralazine	6
Antithrombotic agents	**159 (20.0)**
Anticoagulants	
Warfarin	76
Enoxaparin	7
Rivaroxaban	4
Antiplatelets	
Aspirin	41
Aspirin plus dipyridamole	14
Cilostazol	10
Clopidogrel	7
Statins	**116 (14.6)**
Atorvastatin	82
Simvastatin	25
Rosuvastatin	9
Antimicrobial drugs	**93 (11.7)**
Piperacillin/tazobactam	12
Fosfomycin	12
Levofloxacin	10
Amoxicillin/clavulanic acid	9
Meropenem	9
Ciprofloxacin	7
Vancomycin	7
Ofloxacin	5
Ceftriaxone	4
Ertapenem	4
Others	14
Ambulatory medications	**80 (10.1)**
Colchicine	18
Metformin	10
Alfuzosin	8
Glipizide	7
Finasteride	6
Tamsulosin	5
Levothyroxine	5
Insulin	4
Gliclazide	3
Levodopa/benserazide	3
Others	11
Proton pump inhibitors (PPIs)	**43 (5.4)**
Omeprazole	32
Lansoprazole	7
Rabeprazole	4
Antiepileptic drugs	**33 (4.1)**
Phenytoin	28
Valproic acid	4
Phenobarbital	1
Others	**76 (9.5)**
Senokot	14
Calcium carbonate	10
Lorazepam	9
Ferrous sulfate	9
Acetylcysteine	7
Acetaminophen	6
Metoclopramide	4
Amiodarone	4
Digoxin	3
Piracetam	2
Others	8

may reflect the lack of understanding on differences in plasma concentration profiles of various types of dosage forms along with the lack of knowledge on the hospital's drug formulary of the prescribers. In addition, with inappropriate administration techniques, enteral tube occlusion can occur. Pharmacists can therefore help the stroke team to select the most appropriate drug dosage forms, as well as provide an advice on how best to administer the drugs when an enteral tube feeding is in place. This may include the correct timing of administration to avoid drug-food interaction, appropriate administration technique along with appropriate flushing techniques to avoid incompatibility and tube occlusion issues. Other commonly improper drug selections identified in our study were usage of drugs in the modified Beers Criteria in elderly patients, placing them at high risk of developing drug toxicity.

Drug interactions accounted for 9.9% of the total drug-related problems. Most common medications involved with interactions were anticoagulants (such as warfarin), antiplatelets (such as clopidogrel, cilostazol), anticonvulsant

agents (phenytoin, phenobarbital, sodium valproate) and simvastatin, respectively. Drug interactions can affect patients' clinical outcomes and contribute to increased lengths of hospital stay and healthcare costs. Since some drugs commonly used in a stroke unit (such as warfarin, phenytoin, sodium valproate) were with narrow therapeutic index, a thorough and regular review of drug interactions in a stroke unit especially among these high risk drugs should be implemented as the standard of pharmacy practice in this area.

Adverse drug reactions accounted for 7.7% of the total drug-related problems encountered in our study. Almost two-thirds of the reactions implicated cardiovascular drugs, including antiplatelet agents, anticoagulant agents and antihypertensive drugs. Examples were warfarin-induced upper gastrointestinal bleeding; aspirin plus dipyridamole ER or cilostazol-induced headache/tachycardia; and antihypertensive drug-induced hypotension. All such potentially detrimental drug reactions should be carefully monitored and managed accordingly, especially in the elderly, who are at heightened risk of deleterious effects.

Other drug-related problems were drug use without indications, drug duplications and prescribing errors. Those problems could be minimized by the presence of pharmacists working in collaboration with other healthcare providers to identify and resolve such problems by regularly reviewing the drug therapy.

Our study has several strengths. First, our study had a large sample size of over 800 patients compared to previous studies. As a result, the findings were relatively robust. Second, the acceptance rate of pharmacist's intervention was high which may indicate the high quality of our intervention. Third, the study site is one of the leading university hospitals that is well known throughout Southeast Asia. As a result, other hospitals in the region may use our study as a reference to replicate the pharmacy service in a stroke unit.

In terms of pharmacists' interventions, our study reported a very high rate of physician's acceptance. This may reflect the long-standing relationship and trust that the clinical pharmacists gained from the multidisciplinary team. It is important to note that the all pharmacists who provided interventions received significant amount of training and were supervised by the senior board certified pharmacotherapy specialist. As a result, the results of our study cannot be automatically applied and generalized to untrained pharmacists. Appropriate training should be provided to a pharmacist prior to commencing the work in this specialized unit.

Another major limitation of our study is the lack of control. As a result, we were unable to compare the types and incidences of DRPs in a stroke unit with or without clinical pharmacists. However, we still believe that our study shed some lights on the common types of DRPs in a stroke unit. In addition, it is possible that physicians could have optimized some of the drug therapy issues without the support of pharmacists. Nevertheless, having pharmacist support on a ward round can help prevent DRP from occurring or help reduce the exposure to DRP due to a timely intervention of a pharmacist. Further research work, most preferably, in a multi-centered, randomized, controlled trial fashion comparing usual care versus stroke pharmacy service should be implemented to confirm the benefit of the service.

Conclusion

This study indicates that DRPs are very common in a stroke unit. Characteristic of stroke patients make some of these DRPs unique. Clinical pharmacists can effectively identify and resolve DRPs in a stroke unit. Key functions that pharmacists should provide to the team include medication reconciliation, provision of appropriate drug selection especially when stroke patients are placed on enteral tube feeding, drug interaction management, and dosage adjustment. With the addition of a clinical pharmacist in a stroke care team, drug therapy in this setting can be optimized for the improvement of quality of care for stroke patients.

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