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Regional Variance of the Early Use of Tolvaptan for Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background The development and prompt dissemination of the first drug against a particular disease can contribute to improvements in national health status and medical economy end points and are assumedly affected by socioeconomic factors that have yet to be analyzed. Tolvaptan, a vasopressin receptor 2 antagonist, was developed to treat hyponatremia, congestive heart failure, and cirrhosis ascites, although the approved indications may differ among countries. In Japan, high-dose tolvaptan tablets were approved as the first drug for autosomal dominant polycystic kidney disease (ADPKD) in 2014. This study aimed to better understand the factors that influence the total number of regional prescriptions of tolvaptan for ADPKD since its launch.

Methods The National Database of Health Insurance Claims and Specific Health Checkups of Japan Open Data was used as a national claim-based database. In each of the 47 prefectures in Japan, the total prescribed number of 30 mg tolvaptan tablets between 2015 and 2017 was examined. The parameters explaining the prescription variation among regions were then examined by correlation analysis.

Results Prescriptions for high-dose tolvaptan increased substantially 2 years after the drug's approval; however, the increase differed by approximately 21-fold between regions. Population density was positively associated with prescribed 30 mg tolvaptan tablets per 1000 population in 2015 ($r=0.47$, $P<0.001$). In addition, the increase in prescribed number of tablets per 1000 population was correlated with population density in 2016–2017 ($r=0.30$, $P=0.04$).

Conclusions This macro perspective analysis revealed an urban-rural inequity in prescriptions for the newly approved drug for ADPKD. Further studies are needed to elucidate the factors affecting the geographic variation.

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Introduction

Once a new drug is officially approved for clinical use, its adoption and use may vary among doctors. Accumulating evidence has revealed several factors that appear to influence a physician's decision to start a patient on a new medicine, including peer doctor and expert opinion (1), personality (2), being a specialist of the field (3), prescribing a higher volume in the therapeutic class of the new drug (4), and exposure to information provided by the pharmaceutical industry (5). However, few studies have analyzed the early prescription of the very first drug for a particular disease.

Tolvaptan, a vasopressin receptor 2 (V2) antagonist, has diuretic actions associated with water diuresis rather than natriuresis and was developed as a drug for hyponatremia and fluid retention. Tolvaptan was approved by the US Food and Drug Administration in 2009 as a competitive V2 antagonist for the treatment of hyponatremia associated with congestive heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone secretion. In Japan, the drug, at a maximum dose of 15 mg, was approved in 2010 for fluid retention due to heart failure, with further approval in 2013 for fluid retention due to liver cirrhosis.

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common Mendelian disorders and is estimated to occur in about 25 out of 10,000 people in the general population (6,7). ADPKD is characterized by multiple renal cysts and gradual decline of renal function, progressing to ESKD. Other manifestations include hypertension, liver cysts, and cardiac valve disease (8,9). Following a study demonstrating the effectiveness of mozavaptan (OPC-31260, a prestage drug for tolvaptan) in animals with multiple cystic kidney disease (10), an international clinical trial with a target population of 1445 patients with ADPKD was conducted in 2007 to investigate the efficacy and safety of tolvaptan (TEMPO 3:4 trial) (11). It was reported that the increased rate of kidney volume and the decrease in renal function were slowed down by approximately 50% and 30%, respectively, in the fall of 2012 (11). This led to the approval of tolvaptan as the first therapeutic agent for ADPKD, and its clinical use began in May 2014 in Japan. Subsequent approval of

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the drug occurred in Canada and Europe in 2015, followed by the United States in 2018. The dose used for ADPKD treatment is relatively high compared with that for fluid retention. In Japan, it is recommended to start at 60 mg per day (45 mg in the morning, 15 mg in the evening), with a gradual increase to 90 mg per day (60 mg in the morning, 30 mg in the evening), and then to 120 mg per day (90 mg in the morning, 30 mg in the evening), which was the dosing protocol adopted in TEMPO 3:4 trial (11). Given the potential for fatal adverse effects, including hypernatremia and liver dysfunction, administration of high-dose tolvaptan for ADPKD treatment needs to be started in an inpatient setting, which is unique to Japan. In addition, physicians that prescribe high-dose tolvaptan are required to complete predefined electronic learning resources, and pharmacies are required to confirm the license of the prescribing physician.

The entire population of Japan is covered by a social health insurance system, and the prices and fees of various healthcare services are uniformly set regardless of the type or location of the healthcare provider. As such, patients are free to choose which providers to visit. The coinsurance rate is uniformly fixed at 30%, except for the elderly and children. In 2009, the Ministry of Health, Labor, and Welfare started to construct the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB). The NDB includes >95% of the nationwide medical claims from hospitals and physicians' offices and dental and pharmacy claims. Aggregate table data created from the NDB, which are called NDB Open Data, are anonymized and publicly disclosed. A variety of clinical ecologic studies have been published on the basis of the claim database (12–17). The NDB Open Data does not provide the application of prescriptions; however, the use of 30-mg tablets of tolvaptan is restricted to ADPKD. Moreover, 60-mg and 90-mg tablets are not available in Japan, and patients with ADPKD treated with tolvaptan mainly consume 30-mg tablets. Considering the state of the Japanese national universal health insurance coverage, monitoring the overall spread of the novel treatment for ADPKD by determining the prescribed number of tolvaptan 30-mg tablets is possible.

Under the hypothesis that the characteristic feature of the therapy may be influenced by socioeconomic factors, resulting in regional variations, the primary purpose of this study was to geographically investigate patterns of high-dose tolvaptan prescriptions. The secondary purpose was to investigate domestic regional variations in this clinical practice pattern and possible contributing factors.

Materials and Methods

Database

The NDB Open Data (fiscal year 2015, 2016, and 2017), created by the Ministry of Health, Labor, and Welfare, was used as the data source (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html [in Japanese], accessed December 12, 2019) for the total prescribed number of tolvaptan tablets. In Japan, oral intake agents prescribed by hospital (clinic) outpatient services are dispensed either in the hospitals (clinics) or by out-of-hospital pharmacies, and the database provides prescription data separately for these dispensing agencies. Both in-hospital and out-of-hospital outpatient prescriptions and hospitalized patient prescriptions were included in our analysis. Prescribed tablets <1000 per year were presented as zero in each data set.

Prefectural medical institutional variables and economic and welfare conditions were obtained from the Statistical Observations of Prefectures 2018 provided by the Statistical Bureau, Ministry of International Affairs and Communications (http://www.stat.go.jp/english/data/shihyou/). Data for the fiscal years 2015–2017 were included in this report.

The number of certified nephrologists was based on the registry of Board Certified Nephrologists of the Japanese Society of Nephrology on May 14, 2019, provided by the Japanese Society of Nephrology (https://www.jsn.or.jp/specialist/listindex.php [in Japanese]). The number of certified urologists was based on the registry of the Japanese Board Certified Urologists on November 27, 2019, provided by the Japanese Urological Association (https://www.urol.or.jp/specialist/list/ [in Japanese]).

Ethical Committee Approval

Our project was approved by the investigational review board of the Graduate School of Medicine, University of Tokyo (#11612). The entire protocol of this study was designed in accordance with the Helsinki Declaration.

Statistical Analyses

Relationships between the prescribed number of tolvaptan tablets per 1000 population of each prefecture and potential predictor variables were assessed by Pearson correlation analysis. All statistical calculations were performed using the JMP Pro software version 13.0 (SAS Institute Inc., Cary, NC).

Results

Tolvaptan Prescriptions Increased from 2015 to 2017

Since tolvaptan was approved for ADPKD treatment in 2014, the 30-mg tolvaptan tablet count prescribed nationwide increased by more than three times, from 500,550 to 1,533,885 from 2015 to 2017. In addition, our findings indicated substantial variation in the prescribed number of tablets in different prefectures (Figure 1A). Assuming that disease prevalence is equal among the prefectures, prescribed tolvaptan tablets per 1000 population of each prefecture were evaluated and are presented in Figure 1B. There was a 21-fold difference in the prescribed number of tolvaptan tablet per 1000 population between the most prescribed prefecture (Tokyo) and the least prescribed prefecture (Oita) in 2017.

Regional Factors Determining the Prescribed Number of Tolvaptan

To identify the regional factors contributing to the initial decision to prescribe tolvaptan in 2015, the association of prescribed number of tolvaptan 30-mg tablets with several socioeconomic parameters was analyzed. Total population and population density were positively correlated with the prescribed number of tablets per 1000 population in 2015 ($r=0.48$, $P<0.001$ for total population; $r=0.47$, $P<0.001$ for

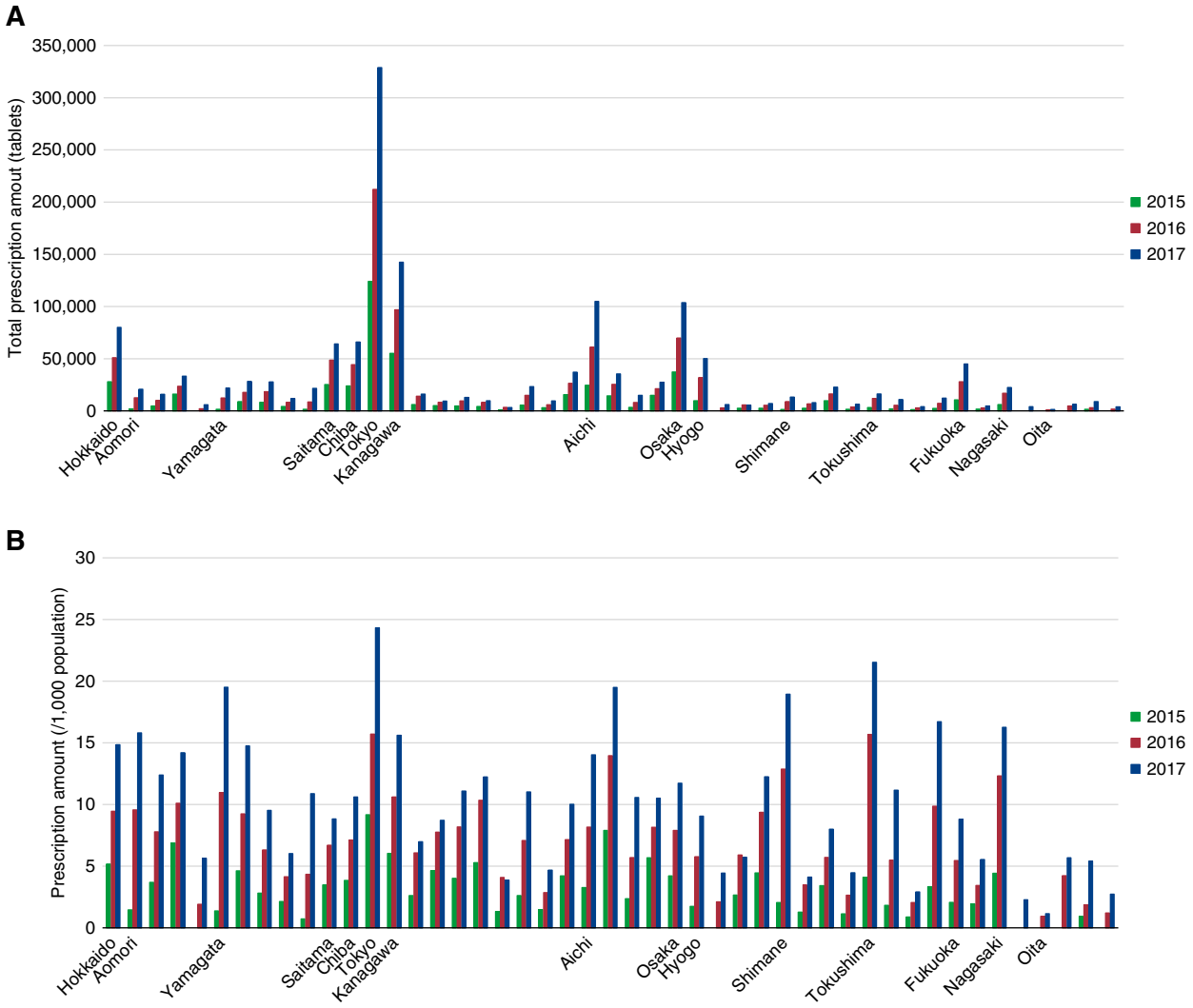

Figure 1. | **Regional variation is observed in prescriptions of 30-mg tolvaptan tablets from 2015 to 2017.** (A) The total prescribed tablets and (B) the prescribed number of tablets per 1000 population are presented.

population density). The number of general hospitals per habitable area, the ratio of the population aged 65 years old and above, and the national medical expenses per capita were positively or negatively correlated with the prescribed number of tolvaptan tablets per population (Table 1). Because all of the factors listed above are assumed to be related to population density, or urban-rural inequity, the partial correlation coefficient considering the population density was evaluated. Indeed, all of the factors turned out to be insignificant after considering population density (Table 1).

Both 2016 and 2017 saw a significant correlation between the prescribed number of tablets per 1000 population and the population density (Figure 2, A–C); however, the values of the correlation coefficient decreased to $r=0.32$ ($P=0.03$) in 2016 and $r=0.34$ ($P=0.02$) in 2017.

Regional Factors Determining the Increase in Tolvaptan Prescriptions

Since tolvaptan was approved for ADPKD treatment in 2014, there has been a substantial growth in the prescribed number of tolvaptan tablets as stated above. Next, we evaluated the variation in the growth among the different regions in Japan. The increase in the prescribed number of tablets per 1000 population showed weak correlation with population density in the time period from 2015 to 2016 ($r=0.08$, $P=0.59$; Figure 3A). However, a strong correlation was again observed in the time period from 2016 to 2017 ($r=0.30$, $P=0.04$; Figure 3B). This difference may be because prefectures with low population densities (such as Tokushima, Shimane, Yamagata, Aomori, and Nagasaki) exhibited large increases in the prescribed number of tolvaptan tablets per 1000 population in the time period from 2015 to 2016. However, these increases were not maintained in the following year, with the exception of the Yamagata prefecture.

Discussion

Prescriptions of high-dose tolvaptan, approved recently as the first disease-modifying agent for ADPKD treatment in Japan, continuously increased in the first 3 years after the

Table 1. Correlation coefficients and partial correlation coefficients, considering population density, among various parameters and the prescribed number of 30-mg tolvaptan tablets per 1000 population in each prefecture in 2015

Parameters	Correlation Coefficent	*P* Value	Partial Correlation Coefficient (Population Density)	*P* Value
Population (thousand)	0.48	<0.001[a]	0.15	0.31
Population density (/habitable area km^2)	0.47	<0.001[a]	—	—
Number of medical doctors (/100,000 population)	0.05	0.76	—	—
Number of hospital beds (/100,000 population)	−0.24	0.10	—	—
Number of general hospitals (/100,000 population)	−0.25	0.09	—	—
Number of general hospitals (/habitable area 100 km^2)	0.40	<0.01[a]	−0.13	0.40
Total household income (1000 JPY/mo)	0.09	0.55	—	—
Average life expectancy (0 yr old, female) (yr)	0.05	0.76	—	—
General population >65 yr old (ratio)	−0.31	0.03[a]	−0.05	0.72
Number of certified nephrologists (/1000 population)	0.26	0.07	—	—
Number of certified urologists (/1000 population)	−0.18	0.22	—	—
Medical expenses (/capita)	−0.29	0.04[a]	−0.19	0.19

General hospitals refer to all the hospitals except for psychiatric hospitals. Habitable area refers to the land area excluding that of forests and lakes.
[a]$P<0.05$.

health policy decision. In this study, we elucidated that the prescribed number of tolvaptan tablets during the period differed substantially among the 47 prefectures in Japan, with the first-year number exhibiting an association with population density. The growth in the prescription number continued this trend in the second to third years, but not in the first to second years of adoption.

Previous studies have emphasized several factors underlying whether doctors will prescribe a new medicine, including peer doctor and expert opinion (1), personality (2), being a specialist of the field (3), prescribing a higher volume in the therapeutic class of the new drug (4), and exposure to information provided by the pharmaceutical industry (5). Our current epidemiologic study casts light on the diversity of the population density. In other words, urban-rural inequity may affect the total number of regional prescribed tablets for a newly approved drug. Indeed, several reports have indicated that urban practices tend to adopt new drugs earlier than rural practices (4,18,19). In addition, physicians in rural areas may have less opportunity to be visited by pharmaceutical sales representatives because of geographic inaccessibility or the doctors' preferences to practice in rural areas (20). In urban areas, greater opportunities exist to communicate with doctors in other hospitals and/or attend meetings focused on novel treatments and related academic subjects.

On the other hand, access to hospitals (number of general hospitals per habitable area) and the number of nephrology and urology specialists were not found to be significantly associated factors. Although ADPKD is one of the most common genetic diseases, specialists who are familiar with the treatment of ADPKD are limited to only a small fraction of nephrologists and urologists. Furthermore, these specialists may be cautious in adopting novel therapies, and their desire to increase the dose of a drug may vary.

Overall, the increase in prescriptions for tolvaptan per 1000 population was maintained between 2015–2016 and 2016–2017, indicating tolvaptan treatment is still in the spreading phase, with the total prescribed number of tablets expected to continue to increase. Although data for only 3 years were available in this study, the tendency for this novel treatment to be concentrated in rural areas seems to be observed not only in 2015 but also in the following 2 years. Because ADPKD is a slowly progressing disease and requires several years to assess the treatment effect of tolvaptan, longer time periods may be required to observe changes in the overall prescription patterns. Another possibility is that an extensive number of prescribed tablets in urban areas may not be a characteristic of the early adoption of a newly approved drug, but rather a characteristic of the treatment itself. Application for tolvaptan treatment is restricted to patients with ADPKD, and patients must be hospitalized upon initiation of the therapy in Japan. Moreover, only physicians that have completed the electronic learning resources are allowed to prescribe high-dose tolvaptan.

Our paper has several limitations. First, the actual number of patients with ADPKD indicated for tolvaptan was unknown. In addition, this analysis was conducted under the hypothesis that the prevalence and severity of ADPKD are uniform throughout the country. Although the number of designated intractable disease recipient certificate holders for ADPKD is available at the Intractable Diseases Research Foundation/Japan Intractable Diseases Information Center website, the number of certified patients was strongly correlated to the prescribed number of high-dose tolvaptan

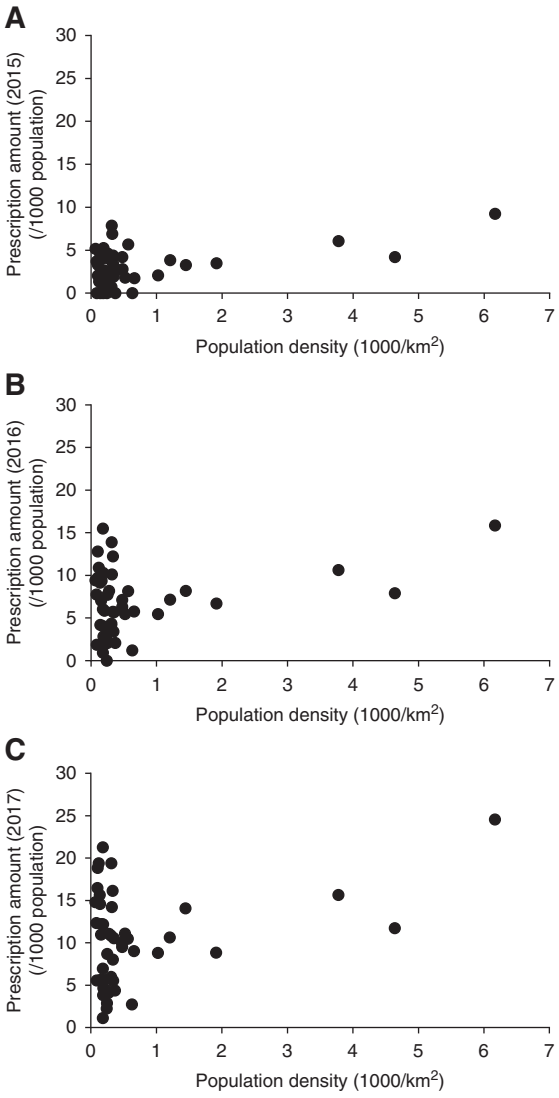

Figure 2. | Positive correlation is observed between prescribed number of 30-mg tolvaptan tablets per 1000 population and population density. (A) 2015, (B) 2016, and (C) 2017.

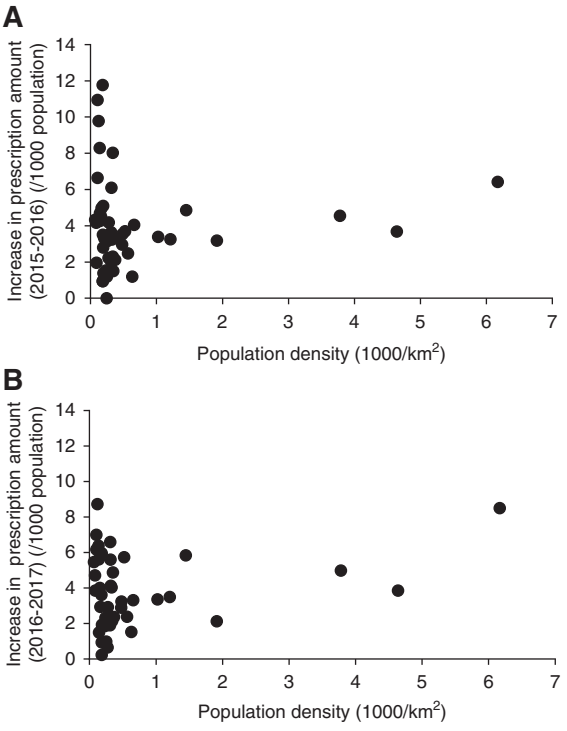

Figure 3. | Positive correlation is observed between the increase in prescribed number of 30-mg tolvaptan tablets per 1000 population and population density for 2016–2017 but not for 2015–2016. Absolute increases in prescribed tablets for the time periods of (A) 2015–2016 and (B) 2016–2017 are adjusted by 1000 population of each prefecture.

tablets (r=0.96, P<0.001). These data support the fact that certification of an intractable disease is provided to alleviate the financial burden on patients who receive high-dose tolvaptan. Daily consumption of 120-mg tolvaptan costs about JPY 4,380,000 (approximately USD 40,000) per year as of December 2019, accounting for almost 20% of the average family income in Japan, where 30% of the costs (JPY 1,300,000) were borne by the patient. With the certification of intractable disease, the self-pay burden is reduced to JPY 30,000 or less according to the patient's income. Second, data were not available for the number of patients currently receiving tolvaptan. Although 90–120 mg per day (consuming two to four tablets of 30 mg tolvaptan per day) of tolvaptan is recommended, it is speculated that a considerable number of patients in Japan are receiving 60 mg per day (mostly consuming four tablets of 15 mg tolvaptan per day). This study focused on the total amount of tablets, and there was no guarantee that the data reflected the number of patients receiving the therapy. Third, this analysis analyzes parameters by prefecture, the first level of administrative division of Japan. Understanding patterns of ADPKD care for patients based on smaller regions or referral centers could provide further clarification.

In conclusion, our findings indicate that, although Japan has universal coverage for prescription drugs, the usage of a new drug differs among regions, partially because of urban-rural inequity. Further studies are needed to elucidate the factors that guide the early adoption and use of new drugs.

Disclosure

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Author Contributions

D. Inoue and R. Inoue were responsible for data curation; R. Inoue was responsible for formal analysis; K. Honda and M. Nangaku reviewed and edited the manuscript; R. Inoue and H. Nishi conceptualized the study and wrote the original draft; and M. Nangaku provided supervision.

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