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Original Article

Clozapine Use in Japan Based on National Database of Health Insurance Claims and Specific Health Checkups Open Data: Disparities by Region, Age, and Sex

Sayako HIGUCHI^{1,2}, Akahito SAKO², Tadayuki KONDO³, Shun KUSANISHI³, Tetsuro ENOMOTO³, Tatsuro HAYAKAWA³, Hidekatsu YANAI², Kensuke YOSHIMURA⁴

1 Department of Psychiatry, National Center of Neurology and Psychiatry

2 Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine

3 Department of Psychiatry, Kohnodai Hospital, National Center for Global Health and Medicine

4 Center for Next Generation of Community Health, Chiba University Hospital

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Abstract

【 Objective 】 Clozapine (CLZ) is an essential drug for the management of treatment-resistant schizophrenia and was approved in Japan in 2009. Previous studies reported the underuse of CLZ and regional disparities in its use in Japan. We aimed to elucidate the clinical epidemiology and real-world use of CLZ in Japan using National Database of Health Insurance Claims and Specific Health Checkups (NDB) Open Data.

【 Methods 】 The NDB covers more than 95% of all administrative claims data from the national health insurance system in Japan. The Ministry of Health, Labour and Welfare provides an open-access version of the NDB (NDB Open Data) covering fiscal year (FY) 2014 to FY2018. The data include the total number of CLZ prescriptions for inpatients and the total number of service fees for management of both inpatients and outpatients

using CLZ stratified by Japan's 47 prefectures, age, and sex. We estimated the number of patients using CLZ based on the number of service fees for patient management.

【Results】 The annual number of 100-mg CLZ tablets prescribed to inpatients in Japan increased from 0.8 million in FY2015 to 1.7 million in FY2018. In FY2018, data on 25-mg CLZ tablets were also available, and CLZ prescriptions totaled 155 mg per 1,000 population. The estimated number of patients using CLZ increased from 1,330 in FY2014 to 3,254 in FY2018. Outpatients accounted for 50.3% in FY2014 and 55.3% in FY2018. In terms of regional disparities, Okinawa prefecture had the largest number of CLZ prescriptions (6,290 mg per 1,000 population) and Shimane prefecture had the smallest (350 mg per 1,000 population). Miyazaki prefecture had an estimated 13.4 patients using CLZ per 100,000 population versus 0.64 in Saitama prefecture. Based on data from the Clozaril Patient Monitoring Service, in FY2018 the estimated number of patients using CLZ per hospital was 14.1 in Okayama prefecture and 0.75 in Shimane prefecture. By sex, the estimated number of patients using CLZ per 100,000 population in FY2018 was 2.8 among men and 2.4 among women. In both sexes, the age group with the largest number of patients using CLZ was 35 to 39 years (7.2 and 6.6 per 100,000 population among men and women, respectively). The average CLZ dose in inpatients was 387 mg in men and 348 mg in women.

【Discussion】 As NDB Open Data summarizes administrative claims data, there are several limitations. However, these data can be used to capture real-world use of CLZ nationwide. This study revealed the clinical epidemiology and regional disparities of CLZ use in Japan. Although the number of patients using CLZ has been increasing, this number is considerably smaller in Japan than in other countries due to delayed approval and strict regulations.

Keywords: clozapine, schizophrenia, NDB Open Data Japan, regional differences, real world data

Introduction

Clozapine (CLZ) is the only antipsychotic indicated for the treatment of treatment-resistant schizophrenia. Treatment resistance is defined as an inadequate response to

two or more antipsychotic drugs given in sufficient doses and for a sufficient duration, or the inability to increase the dose of antipsychotic drugs to a sufficient level due to side effects (23).

CLZ was approved worldwide in 1969

as an atypical antipsychotic causing fewer extrapyramidal symptoms, side effects often seen with antipsychotic drugs, but its marketing and development trials were discontinued in 1975 due to agranulocytosis, a serious side effect. However, it was proven that a significant number of patients with treatment-resistant schizophrenia responded to CLZ, and CLZ was launched in Japan in 2009 with the indication limited to treatment-resistant cases 24). CLZ has a variety of serious side effects, including agranulocytosis, myocarditis, cardiomyopathy, and hyperglycemia. The Clozaril Patient Monitoring Service (CPMS) was introduced at the same time as the launch of CLZ for the early detection and treatment of agranulocytosis and glucose intolerance when they occur. This service registers healthcare professionals, medical institutions, insurance pharmacies, and patients who use CLZ, and supports reliable monitoring of white blood cell counts, neutrophil counts, and blood glucose levels for each patient 29).

In many cases, hematological disorders such as agranulocytosis occur in the early stages of administration, and in principle, it is recommended that patients be kept under inpatient care for the first 18 weeks of administration 25). According to CPMS operational procedures 2), blood tests

are required to be conducted once a week from the start of administration until 26 weeks, and then once every two weeks thereafter even if certain conditions are met. If agranulocytosis or fever is observed, a hematologist should be consulted immediately and the patient should be treated according to the manual. In addition, patients are classified into three categories based on blood glucose tests, and in the case of "diabetes or strongly suspected diabetes" criteria, blood glucose levels should be measured every two weeks and HbA1c every four weeks, and the appropriateness of CLZ administration should be discussed with a diabetes physician. Frequent blood tests and collaboration with internists make the operation much more complicated than with other antipsychotic drugs.

According to the 2017 patient survey by the Ministry of Health, Labour and Welfare, the number of schizophrenia patients being treated at medical institutions in Japan was 790,000 13), of which 20 ~ 30% were estimated to be treatment-resistant 17). Based on this, the number of treatment-resistant schizophrenics is estimated to be about 160,000 to 240,000, and some estimate that the number of patients who can consent to CLZ treatment is 30,000 of them 4). The total number of patients registered with CPMS 2) from 2009 to May 2020 was 10,266, and according to

the Mental Health Welfare Data 14)32), the total number of patients who used CLZ in FY2017 was 3,921, including both out- and inpatients.

It is possible that patients who have the potential to be treated with CLZ are not being adequately treated in Japan, and that the number of patients prescribed CLZ is markedly lower than in other countries. In addition, the number of patients registered with CPMS by prefecture 2)30) suggests that there may be significant regional differences. The purpose of this study was to clarify the actual status of CLZ use by prefecture, sex, and age group, mainly using "National Database of Health Insurance Claims and Specific Health Checkups (NDB) Open Data" 12) provided by the Ministry of Health, Labour and Welfare.

I. Research Methods

1. NDB Open Data Japan (NDB Open Data)

The information accumulated in the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) contains information that is useful for improving health and optimizing medical costs, and has been used in various studies because it allows detailed analysis on a patient-by-patient basis 5)26). On the other hand, an adequate research environment and data-handling skills

are necessary to use NDB, and the Ministry of Health, Labour and Welfare has provided NDB Open Data, which can be obtained and analyzed more easily by a wide range of entities, and it was used in this study 12). NDB Open Data is available from the first NDB Open Data released in FY2016 (receipt information for FY2014 and specific health checkup information for FY2013) to the fifth NDB Open Data released in FY2020 (receipt information for FY2018 and specific health checkup information for FY2017) at the time of writing this paper. The information is divided into six major categories: "medical treatments," "dental treatments," "dental diseases," "prescription drugs," "specific health checkups (laboratory test values)," and "specific health checkups (standard questionnaires)". In particular, "medical treatments" are based on medical in-/outpatient and DPC receipts, and numbers of calculations for each medical treatment divided in the score table notified by the Ministry of Health, Labor and Welfare are aggregated "by prefecture" and "by sex and age group". The prefecture is identified by the address of the medical institution and pharmacy, not the patient's address. "Prescription drugs" are aggregated based on medical in-/outpatient, DPC, and dispensing receipts by "oral," "topical," and

"injection" dosage forms, and by "prefecture" and "sex and age group." Based on the standard unit of National Health Insurance drug price listing, the drugs with the largest number of prescriptions by drug category are published, with the first edition being the top 30 drugs in terms of the number of prescriptions per year nationwide, and the second edition being the top 100 drugs. The number of prescriptions by prefecture, sex, and age group is not published if it is less than 1,000. For example, if the number of inpatient prescriptions of CLZ 100-mg tablets in a prefecture is less than 1,000 per year, the number of prescribed tablets in that prefecture will not be published. Similarly, the number of calculations of additions, etc., is not disclosed if less than 10 for a single item. If there is only one prefecture or age group for which the number of prescriptions or calculations for a certain drug or calculation is undisclosed because of its low frequency, the undisclosed items can be calculated from the total number of prescriptions and calculations and the sum of other items. For this reason, the entire data set was undisclosed the first four times, and two locations showed low frequencies the fifth time. A number of studies based on NDB open data have been published, including in the field of neuropsychiatry (15)(27)(33).

2. Analysis Method

In this study, we used the number of CLZ 100-mg-equivalent prescriptions, which was calculated by summing the number of hospitalized prescriptions of Clozaril® 100-mg and 25-mg tablets obtained from NDB Open Data, and the number of times the treatment-resistant schizophrenia treatment guidance and management fee (hereafter, management fee) was calculated as an indicator of the actual condition of CLZ prescription.

The package insert (25) for CLZ states that the initial dose is 12.5 mg per day and is gradually increased to 200 mg per day, with a maintenance dose of 200 to 400 mg per day and maximum dose of 600 mg per day. CLZ is available in 100-mg and 25-mg tablets, but the number of prescriptions of 25-mg tablets was small, and data were available only for hospital admissions in FY2017 and FY2018. Data on the number of 100-mg CLZ prescriptions were limited to hospital admissions from FY2015 to FY2018, and no outpatient data were available. Furthermore, data by prefecture were limited to FY2016 and FY2018 only.

The management fee can be calculated only once a month for patients with treatment-resistant schizophrenia who are receiving CLZ. Data for the five years from FY2014 to FY2018 are available separately for in- and

outpatients, and the number of calculations for in- and outpatients combined was used in the analysis. However, data for inpatient admissions by prefecture were not published because there was one prefecture where the number of calculations was less than 10 times in FY2015 2). Since patients using CLZ are required to have a blood test every two weeks 2) and the management fee can be calculated once a month for both in- and outpatients, we estimated the number of patients using CLZ by in- and outpatients based on the number of calculations in each year, assuming that all patients underwent calculations 12 times a year. In addition, the number of prescribed CLZ 100-mg-equivalent tablets was divided by the number of patients (hospitalized) using CLZ, and the number of prescribed tablets/day and dose/day per patient (hospitalized) using CLZ were calculated.

For analysis by prefecture, the number of CLZ 100-mg-equivalent prescription tablets in FY2016 and FY2018, and the number of management fee calculations in FY2014, FY2016, FY2017, and FY2018 were calculated per 1,000 population, respectively. Based on the regional classification of CPMS, we divided Japan into six regions (Hokkaido/Tohoku, Kanto, Chubu,

Kansai, Chugoku/Shikoku, and Kyushu/Okinawa), and calculated the number of times the management fee was calculated per 1,000 population for each region. However, data for Mie, Shimane, and Yamaguchi for FY2014 were not published because the number of calculations was less than 10. In addition, the number of patients using CLZ per 100,000 population was calculated for each prefecture. We also calculated the number of times the management fee was calculated per registered institution in each prefecture in FY2018, using the number of medical institutions that have registered patients with CPMS as of August 2019 2) as the denominator.

For analysis by sex and age group, we calculated the number of CLZ 100-mg-equivalent prescription tablets from FY2015 to FY2018 and number of management fee calculations from FY2014 to FY2018 per 1,000 population and per CLZ-using patient (hospitalized) for males and females (together and separately) in each 5-year age group.

Population estimates as of October 1 for each year published by the Statistics Bureau of the Ministry of Internal Affairs and Communications were used to calculate each of the above indicators.

This study was approved by the Ethics Review Committee of the National

Center for Global Health and Medicine (approval number: NCGM-G-003402).

II. Results

The number of CLZ 100-mg inpatient prescriptions, excluding 25-mg tablets for comparison between years, was 820,000 in 2015, 930,000 in 2016, 1,110,000 in 2017, and 1,710,000 in 2018, approximately doubling over 3 years. Including the 25-mg tablets converted to 100-mg tablets, the number was 1.96 million tablets in FY2018. The number of times the management fee was calculated (in- + outpatient) was 16,000 times in 2014 and 39,000 times in 2018, more than doubling, showing an increasing trend similar to the number of CLZ 100-mg tablets prescribed. The proportion of outpatients increased from 50.3 to 55.3%. The number of patients using CLZ was 1,330 in FY2014 and 3,254 in FY2018, estimated from the number of times the management fee was calculated. The number of prescribed tablets/day per patient (hospitalized) using CLZ was 2.7, 2.6, 2.6, and 3.2 tablets from FY2015 to FY2018, respectively, excluding 25-mg tablets for comparison of each year. When 25-mg tablets were included and converted to 100 mg, the number was 3.7 tablets in FY2018.

The number of CLZ 100-mg-equivalent prescriptions in FY

2018 was 15.5 tablets per 1,000 population. By prefecture (Figure 1), Okinawa had the highest number (62.9 tablets, 4.1-times the national average), followed by Okayama (51.7 tablets, 3.3-times) and Saga (44.7 tablets, 2.9-times), while Shimane had the lowest number (3.5 tablets, 0.23-times the national average), Tokyo (3.7 tablets, 0.24-times), and Saitama (4.0 tablets, 0.26-times). The number of CLZ 100-mg prescriptions in FY2016 was 6.0-times the national average in Okinawa, which had the highest number of CLZ 100-mg prescriptions, while Shimane and Tokushima had fewer than 1,000 prescriptions per year and were not disclosed, suggesting that regional differences are decreasing.

The number of management fees (out- + inpatient) calculated in FY2018 was 22,000 times for outpatients and 17,000 for inpatients, for a total of 0.31 per 1,000 population. By prefecture, the highest number of management fees was calculated per 1,000 population (Fig. 2), with 1.6 times in Miyazaki (5.2-times the national average), followed by 1.1 in Okinawa (3.5-times) and 1.1 in Okayama (3.5-times), and the lowest number was 0.077 in Saitama (0.25-times), followed by 0.093 in Shimane (0.30-times), and 0.094 in Miyagi (0.31-times). In FY2014, Miyazaki had the highest number of management fees (6.6-times the

national average) and Kanagawa had the lowest (0.06-times the national average), indicating that regional differences are decreasing in terms of the number of management fees calculated per population.

The highest number of patients using CLZ per 100,000 population was 13.4 in Miyazaki, 9.3 in Okinawa, and 8.9 in Okayama, and the lowest was 0.64 in Saitama, 0.77 in Shimane, and 0.79 in Miyagi, calculated from the management fee in FY2018. The ratio of out- to inpatients also varied by region, with Akita, Tokyo, and Hyogo having the highest outpatient rates (92, 79, and 72%, respectively) and Kagoshima, Kagawa, and Mie having the lowest (26, 27, and 29%, respectively). Figure 3 shows the number of management fee calculations per 1,000 population by region, with Kyushu and Okinawa showing the highest number of calculations (0.56 calculations per 1,000 population, or 4.7 patients using CLZ per 100,000 population) and Kanto showing the lowest (0.21 calculations per 1,000 population, or 1.7 patients using CLZ per 100,000 population), indicating a threefold difference. The annual trend from FY2014 to FY2018 showed an increase in all regions, but the lowest number in Kanto increased 2.6-fold and the highest number in Kyushu/Okinawa increased 2.3-fold,

indicating that the regional differences are decreasing. However, when compared with the national average, the lowest number in the Kanto region increased from 0.67 to 0.60-times the national average, and the highest number in the Kyushu/Okinawa region increased from 1.8 to 1.9-times the national average, indicating that the regional differences were not consistent.

The number of management fees calculated per medical institutions that had registered patients with CPMS by prefecture (August 2019) in FY2018 was 84.3 (7.0 patients per institution), and the highest number of calculations was 170 in Okayama (2.0-times the national average), followed by 159 in Saga (1.9-times), 157 in 1000 leaves (1.9-times), and the lowest was 9 in Shimane (0.11-times), 22 in Nara (0.26-times), and 26 in Hokkaido (0.31-times) (Fig. 4).

By sex, the number of CLZ 100-mg prescribed tablets from FY2015 to FY2018, excluding 25-mg tablets for comparison of each year, was 7.9, 9.1, 10.8, and 16.7 tablets per 1,000 population for males and 5.0, 5.5, 6.7, and 10.6 tablets per 1,000 population for females, respectively. The number of tablets was higher in males than in females, with an increasing trend in both sexes. When converted to 100-mg tablets including 25-mg tablets, the

number of tablets in FY2018 was 18.9 for males and 12.3 for females. The number of times the management fee was calculated (in- + outpatient) from FY2014 to FY2018 was 0.14, 0.18, 0.22, 0.27, and 0.33 times per 1,000 population for males and 0.12, 0.15, 0.19, 0.24, and 0.29 times for females, respectively, showing an increasing trend over time. The number of patients using CLZ per 100,000 population in FY 2018 was 2.8 males and 2.4 females, and the dose (/day) per hospitalized patient using CLZ was 387 mg for males and 348 mg for females.

By age group, the highest number of CLZ 100-mg-equivalent prescriptions per 1,000 population in FY 2018 (Figure 5) was in the 30-50 age group for both males and females, with 45.4 tablets in the 35-39 age group, the highest among males, and 30.9 tablets in the 45-49 age group, the highest among females. The data were not made available because there were fewer prescriptions than 1,000 tablets for men and women over the age of 0-14 years, 80 years or older for men, and 85 years or older for women. The top three age groups with the highest CLZ use (in- + outpatients) per 100,000 population (Figure 6) were 30-34, 35-39, and 40-44 years for both sexes, with 7.2, 7.2, and 6.4 patients for males and 6.1, 6.6, and 5.4 patients for females in the order of age group. The number of

calculations was less than 10 for both males and females aged 0-14 years and 85 years or older, and therefore not disclosed. The dose (/day) per inpatient using CLZ (Figure 7) was higher for both males and females in the age group 15-19 years, being 457 mg for males and 392 mg for females. The dosage for males was higher than that for females in most age groups, and the dosage was lower in older age groups. The dosage was extremely high for females aged 80-84 years due to the small number of hospitalized patients.

III. Discussion

In this study, both the number of CLZ prescriptions and number of times the management fee was calculated showed an increase, with an estimated 3,254 patients using CLZ in FY 2018, and the use of CLZ increased over time. From FY 2014 to FY 2018, the percentage of outpatients in the number of calculations increased from 50.3 to 55.3%. Although regional differences have been decreasing over time, there were large variations among prefectures, and CLZ use was particularly prevalent in the Kyushu and Okinawa regions in terms of the number of calculations per 1,000 population (in- + outpatient). By sex, the number of patients using CLZ and amount of CLZ administered per inpatient were higher among males.

The number of CLZ 100-mg tablets prescribed and number of calculations peaked in the 30s to 50s for both men and women, and the dosage tended to decrease with age in hospitalized patients.

1. CLZ diffusion

A low prevalence of CLZ use has been reported in many countries, and the differences among countries are also marked. Comparing the frequency of CLZ use per 100,000 population in 2014 in 17 countries including Japan 1), the highest rate was observed in Finland with 189, followed by New Zealand with 116, and in Asia, Taiwan with 88, while Japan was the lowest with 0.6. Since this study included only outpatients, the frequency of use in Japan, with its large number of inpatients, may be underestimated. However, even with our data, the estimated number of patients using CLZ in FY2018 was 2.6 patients per 100,000 population, and compared with other countries, Japan is still lagging far behind. The reasons for this are thought to include a delay in the introduction of CLZs and strict regulations. Although clinical trials were initiated in Japan in 1995 and an application for approval was filed in 2004, the actual launch of CLZ in Japan was not until 2009 18), due to controversy between regulatory authorities and academic societies over

the creation of guidelines for use and the implementation of clinical trials in accordance with these guidelines. This was 19 years later than in the United States. According to a comparison of CLZ regulations in different countries, the frequency of blood monitoring for patients on CLZ maintenance therapy with stable white blood cell and granulocyte counts is every two weeks in Japan, compared with every month in other countries, making Japan's regulations uniquely strict. In addition, while there are multiple pharmaceutical companies handling CLZ in most countries, in Japan there is only one pharmaceutical company, Novartis Pharma, which is considered to be the reason for the slow spread of CLZ in Japan 22).

On the other hand, in this study, the number of CLZ 100-mg prescription tablets approximately doubled over 3 years, and the number of times the management fee was calculated more than doubled over 4 years. The number of patients using CLZ increased from 1,330 to 3,254 from FY2014 to FY2018, and the diffusion of CLZ has been steadily progressing. The spread of CLZs is expected to facilitate the transition of long-term inpatients with psychiatric disorders to the community and shorten the average length of stay in psychiatric beds 4)21). The ratio of outpatients to the total number of

management fee calculations increased from 50.3 to 55.3% overall, although there are large regional differences, and the estimated number of outpatients also increased from 670 to 1,801.

Various revisions have been made to the system in Japan to promote the widespread use of CLZs. The CPMS rules have been frequently revised: in 2014, CLZ prescriptions became available at medical institutions without inpatient facilities due to the establishment of new registered outpatient institutions; in 2017, patients who had discontinued treatment based on discontinuation criteria could be re-admitted if approved by the Clozaril Appropriate Use Committee; and in 2018, it became possible to collaborate with internists other than hematologists 2). In addition, the revision of medical fees in FY2018 made it possible to exclude CLZ drug fees from the scope of Diagnosis Procedure Combination and calculate the fee on a piecework basis for "inpatient fees for psychiatric treatment wards" and "inpatient fees for wards with enhanced community transition functions," which is considered a major factor promoting the increase in patients prescribed CLZs.

Furthermore, in FY2020, medical fees were revised to allow patients who are newly prescribed CLZ to receive

psychiatric emergency inpatient fees even if they are transferred within the same medical institution, and to exclude patients who are newly prescribed CLZ from the rate of transfer to home in psychiatric emergency inpatient fees. This has made it easier to transfer patients to another ward for the introduction of CLZ, and the rate of home transfers has not decreased, even when patients are hospitalized for more than three months or need to be transferred to a hospital. At the same time, a revision was made to allow HbA1c to be calculated separately only once a month for patients receiving CLZ. In June 2021, the CLZ package insert was revised to allow blood monitoring at 4-week intervals after 52 weeks under certain conditions. In addition, the administration criteria were relaxed to allow administration to patients with a history of agranulocytosis or severe neutropenia 25), and CLZ is expected to become more widely used in the future.

2. Dosage of CLZ

The maintenance dose of CLZ ranges from 200 to 600 mg, but the dose (/day) of CLZ per patient (hospitalized) using CLZ in this study in FY 2018 was 370 mg. This includes inpatients during the induction phase, and the dose for patients taking maintenance doses as outpatients may be even higher. In a

study of 3,746 patients enrolled in CPMS from 2009 to 2016 16), the maximum dose for 3,526 patients without leukopenia or neutropenia averaged 387.5 mg. The mean dose for 1,860 newly initiated patients in a post-marketing survey 28) from 2009 to 2015 was 322 mg, which may not differ significantly from our data.

3. Regional differences

It has long been pointed out that there are regional differences in the number of medical institutions that have registered patients with CPMS and number of patients per registered medical institution, and a comparison of the number of medical institutions that have registered patients with CPMS per 100,000 population in each prefecture in FY 2018 showed that the highest number was 1.2 institutions in Miyazaki and the lowest was 0.14 institutions in Saitama 2)30). In this study, a large disparity in the use of CLZ was also observed between prefectures, with Okinawa having the largest number of CLZ 100-mg prescriptions and Shimane the smallest, with a disparity of approximately 18-times. On the other hand, in a study 19) examining regional differences in chlorpromazine equivalents of antipsychotics prescribed as outpatients using NDB open data in FY2015, Nagano, which had the

highest number of prescriptions, had 1.9-times as many as Nara, which had the fewest, and the disparity was not as marked as with CLZ. In FY2018, the number of management fees calculated per registered medical institution for CPMS patients was about 19-times higher in Okayama, the largest, and Shimane, the smallest, showing a large regional difference. Focusing on the ratio of out- to inpatients, the results suggest that Akita and Tokyo, where the ratio of outpatients is higher, have the potential to successfully transition patients with treatment-resistant schizophrenia to the community. Thus, the large regional differences in the number of CLZ prescriptions compared with other antipsychotics may be due not only to regional differences in prevalence and the lack of uniformity in physician practices, but also to regional differences in medical systems, including those for CPMS. The NDB open data only allow analysis by prefecture, but the Regional Mental Health Resources Analyzing Database (ReMHRAD), which uses NDB, analyzes by secondary medical region 32). Regional differences in CLZ prescriptions have also been an issue in other countries, and a study using the French insurance database found that in some regions, CLZs were hardly prescribed at all, while in others they were prescribed nearly six-times more

than the national average 31).

A survey 9) conducted in 2018 among 222 medical institutions that have registered patients with CPMS nationwide showed that the cumulative number of patients per institution was less than 9 in more than half of the institutions, and many institutions do not provide CLZ treatment to a large extent even if they are already registered with CPMS. Regarding barriers to CLZ treatment, more than 30% of the institutions answered that the following were applicable: "Too many blood tests," "complicated input of CPMS," "concern about side effects such as agranulocytosis," "concern about cooperation with hematology, internal medicine treating diabetes, and other physical medicine departments," and "inability to obtain consent from patients or their guardians". The regional differences may be due not only to differences in prescribing attitudes of psychiatrists because of the complexity of CLZ administration at the time of introduction and during administration, but also to differences in medical systems and medical coordination. Six regions were selected as model projects for the Ministry of Health, Labour and Welfare's 2017 project to develop regional cooperation systems for intractable psychiatric disorders: Okinawa, Okayama, Hyogo, Osaka,

Mie, and Chiba. In these regions, base and cooperating hospitals also played a role in the use of CLZs, and a favorable network among hospitals including physical medicine departments was established. In a policy study by Kida et al., hospitals in Miyazaki, Aichi, Yamanashi, Akita, and Okinawa were selected as good-practice hospitals with a large number of CLZ cases 9). These good-practice hospitals had established CLZ committees, treatment manuals, clinical paths, and specialized CLZ wards. The regions with good-practice areas and good-practice hospitals coincide with the prefectures with the highest number of prescriptions and management fees in this study, indicating that regional differences arise depending on whether the environment is conducive to the use of CLZs. We believe that incorporating the innovations and know-how of hospitals 7-9)20) that are actively engaged in CLZ treatment in each prefecture and facility will lead to the resolution of regional differences.

4. Age distribution

The package insert 25) of CLZ states that it should be administered with caution to the elderly, that safety regarding administration during pregnancy has not been established, that lactation should be avoided, and that efficacy and safety in children

have not been established.

In this study, the number of CLZ users was small among minors and elderly patients. Elderly patients are described as follows: "Urinary retention and constipation due to anticholinergic effects are likely to occur, and orthostatic hypotension and tachycardia are also likely to develop, especially in the elderly with a decreased cardiovascular function." Therefore, it is possible that many patients have more difficulty in starting and continuing CLZ compared with other age groups due to a decline in physical function and increased complication rate of physical illness, as well as changes in schizophrenia symptoms associated with aging. A report 1) comparing 17 countries also found that CLZ use peaked between 30 and 59 years of age in most countries, and the average age of the 3,780 Japanese patients registered with CPMS was 40.6 years 6).

Furthermore, it has been reported 3) that the blood concentration of CLZ increases by 4% for every 5-year age increase and decreases by 5% for every 5-year age decrease after 40 years of age, suggesting that the dosage decreases as patients get older. This is consistent with the results of this study.

5. Sex differences

In FY2018, the number of CLZ-using

patients per 100,000 population was 1.2-times higher in males than in females, with males accounting for 53.7% of the 3,780 CPMS-registered patients 6), being slightly higher in males in Japan, but 1.5-times higher in males in data comparing the 17 countries 1).

The dose (/day) per hospitalized CLZ-using patient was 1.1-times higher in males than in females. The blood concentration of CLZ was reported to be 17% higher in females than in males 3), which is consistent with this study. In addition, smoking was reported to induce CYP1A2, a CLZ-metabolizing enzyme, and decrease the blood concentration of CLZ 3)34). According to the National Health and Nutrition Examination Survey 11), the adult smoking rate in FY 2019 was 29.0% for males and 8.1% for females, suggesting that males smoke more than females and thus have higher doses. Furthermore, it was reported that the blood concentration of CLZ decreased by 5% for every 10 kg increase in body weight and increased by 5% for every 10 kg decrease in body weight 3), bordering on an 80-kg body weight, suggesting that males are generally heavier than females and therefore receive higher doses of CLZ.

6. Limitations and strengths of this study

First, unlike the NDB special sampling data, which allow analysis by individual patient (5)26), the NDB open data only provide the number of prescribed CLZ tablets per year nationwide, by prefecture, sex, and age group. Therefore, it is impossible to discern how many patients were prescribed CLZ, how many tablets were administered per patient, and whether prescriptions were started, discontinued, or terminated in the middle of a fiscal year. Although the study was conducted to investigate the problem of CLZ not being prescribed to patients who need it, given its slow diffusion compared with other countries, there were no outcome data such as therapeutic efficacy or side effects, and the risk of excessive or inappropriate use or side effects could not be investigated. However, we were able to estimate the number of patients prescribed and average number of tablets prescribed based on the management fee, which can be calculated once a month for both out- and inpatients, targeting only CLZ-prescribed patients. The estimated number of patients is one for every 12 calculations, and the actual number of patients is likely to be higher considering the number who start or stop in the middle of a fiscal year.

Second, NDB excludes welfare recipients and patients under the

Medical Treatment and Supervision Act, whose medical expenses are covered by public funds. The percentage of welfare recipients is high among schizophrenic patients, and a questionnaire survey (10) conducted at 30 designated inpatient institutions that provide inpatient care for patients under the Medical Treatment and Supervision Act showed more patients using CLZs than those in general psychiatric beds. While the data were prepared as a tabulation table from NDB, NDB open data cover most insurance treatment, and although the data provided are similar to an all-inclusive survey, they exclude the publicly funded patients mentioned above, and the possibility that the results are underestimated cannot be denied.

Third, data are not published when the number of prescribed tablets or number of calculations is small. CLZ is available in both 100-mg and 25-mg formulations, but the number of prescriptions of 25-mg tablets is small, and in some years data are not published because they are not among the top 100 prescribed neuropsychiatric drugs. Data for 100-mg tablets are also not available for outpatient prescriptions because they are not in the top 100 prescriptions. The 100-mg tablets prescribed for inpatients are the main subject of the analysis, but it is not possible to distinguish between

patients who were started on a low dose in the induction phase and those who were already on a maintenance dose but were hospitalized due to side effects and psychiatric or physical problems. The average number of tablets administered to hospitalized patients may be underestimated because it includes those receiving low doses for induction, patients admitted or discharged in the middle of the month, and 25-mg tablets are not included in the data depending on the year.

Finally, the latest data on the number of medical institutions that have registered patients with CPMS are published every month, but historical data are not available. Therefore, the analysis was conducted by combining the FY2018 NDB open data and number of medical institutions that had registered patients with CPMS as of August 2019, which are not accurate data, including the fact that the number of patients has increased over time. In this regard, it would be desirable for historical data on the number of medical institutions that have registered patients with CPMS to be made public in order to comprehend the current situation accurately.

However, the strengths of this study include the following: the NDB open data cover the entire country, allowing analysis at the national level, including changes over time; data that have not

been fully investigated in the past, such as the average dosage for hospitalized patients and actual usage by prefecture, sex, and age group, were obtained; data from existing large-scale studies did not deviate much from those data, and the accuracy of the data was high; there have been no published studies on the actual prescribing of CLZs using NDB open data.

Conclusion

The delay in the spread of CLZs in Japan and regional differences have been discussed for some time, and the results of the present study confirm this. The mean dosage for hospitalized patients using CLZ was also clarified. Furthermore, by sex and age group, the number of patients using CLZ and mean dosage for hospitalized patients using CLZ were higher in males, and the number of prescriptions for children and elderly patients was lower, with peaks in the 30s and 40s. Although the number of CLZ prescriptions has been decreasing over time, there is a marked disparity between prefectures, but the use of CLZ is steadily increasing and is expected to equalize in the future.

An abstract of this study was presented at the 116th Annual Meeting of the Japanese Society of Psychiatry and Neurology in Sendai by residents and undergraduate students.

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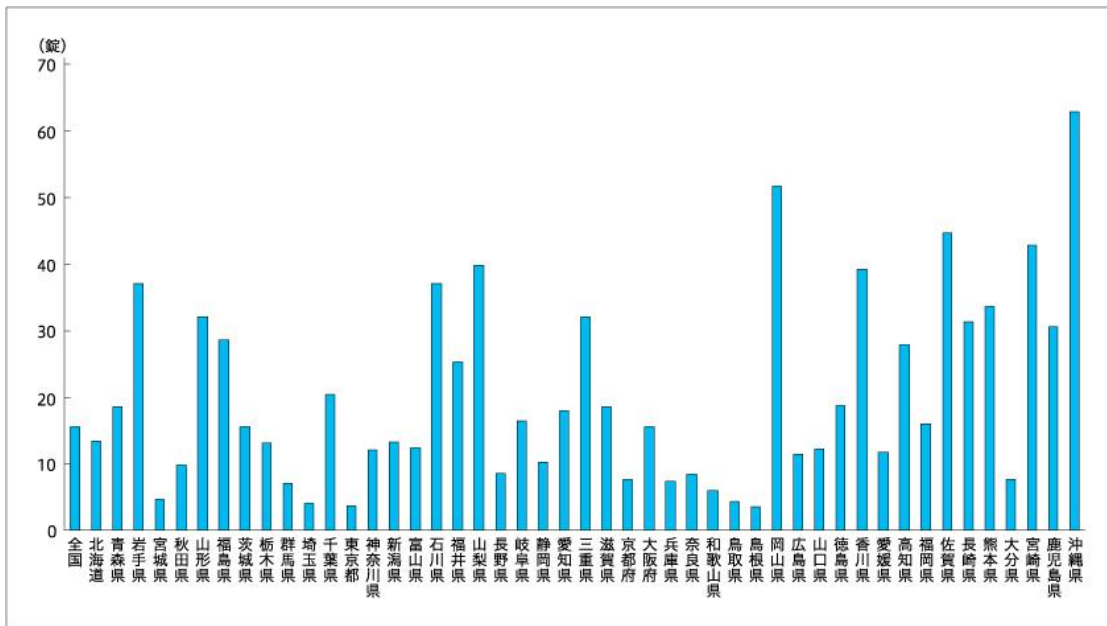


図1 2018年度人口千人あたりCLZ 100 mg錠換算入院処方錠数

Figure 1: Number of CLZ 100-mg-tablet-equivalent inpatient prescriptions per 1,000 population in FY 2018

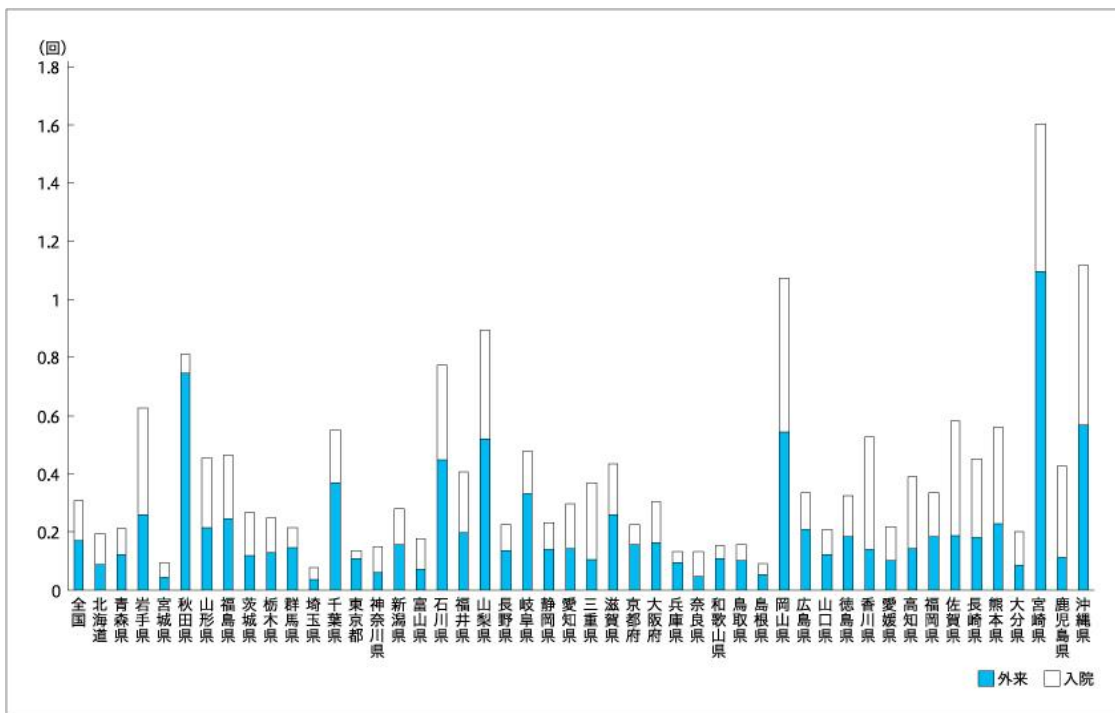


図2 2018年度人口千人あたり管理料算定回数

Figure 2: Number of management fee calculations per 1,000 population in FY 2018

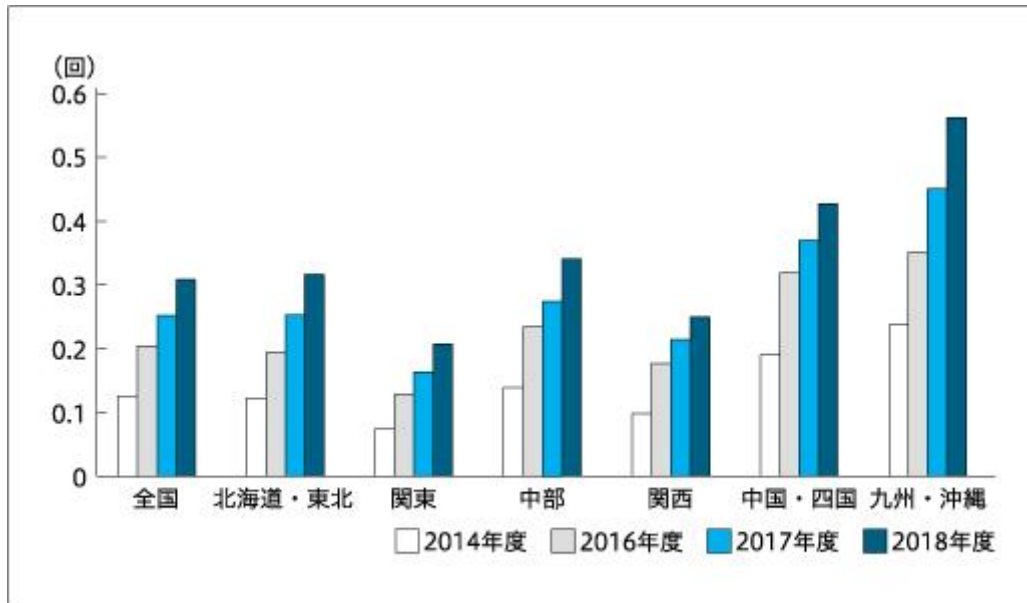


図3 地方別人口千人あたりの管理料算定回数（外来+入院）

Figure 3: Number of management fee calculations per 1,000 population by region (out + inpatient)

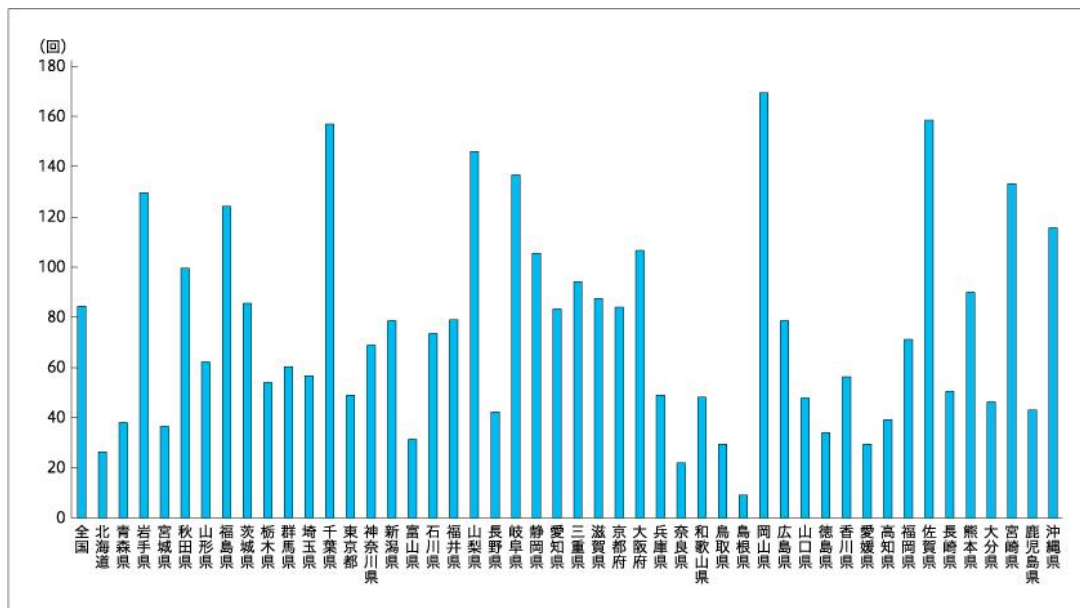


図4 2018年度管理料の算定回数（入院+外来）/2019年8月時点のCPMS患者登録済み医療機関数

Figure 4: Number of management fee calculations in FY 2018 (in + outpatient)/Number of medical institutions that had registered patients with CPMS as of August 2019

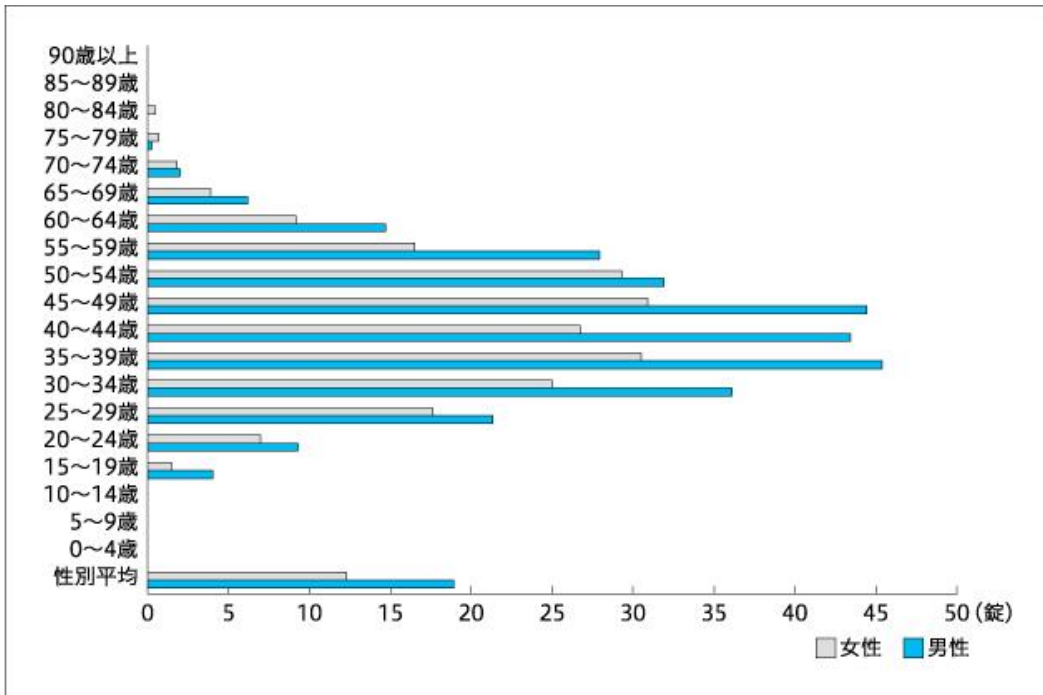


図5 2018年度人口千人あたりCLZ 100mg換算入院処方錠数(性・年齢階級別)

Figure 5: Number of CLZ 100-mg-equivalent inpatient prescription tablets per 1,000 population in FY 2018, by sex and age group

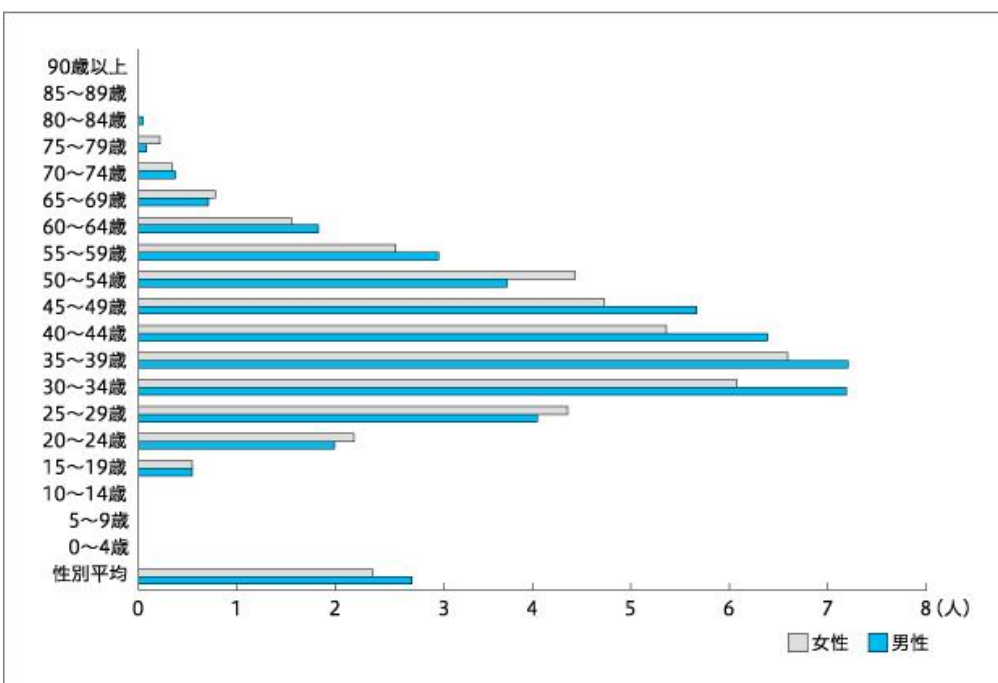


図6 2018年度人口10万人あたりCLZ使用患者数(性・年齢階級別)

Figure 6: Number of patients using CLZ per 100,000 population in FY 2018, by sex and age group

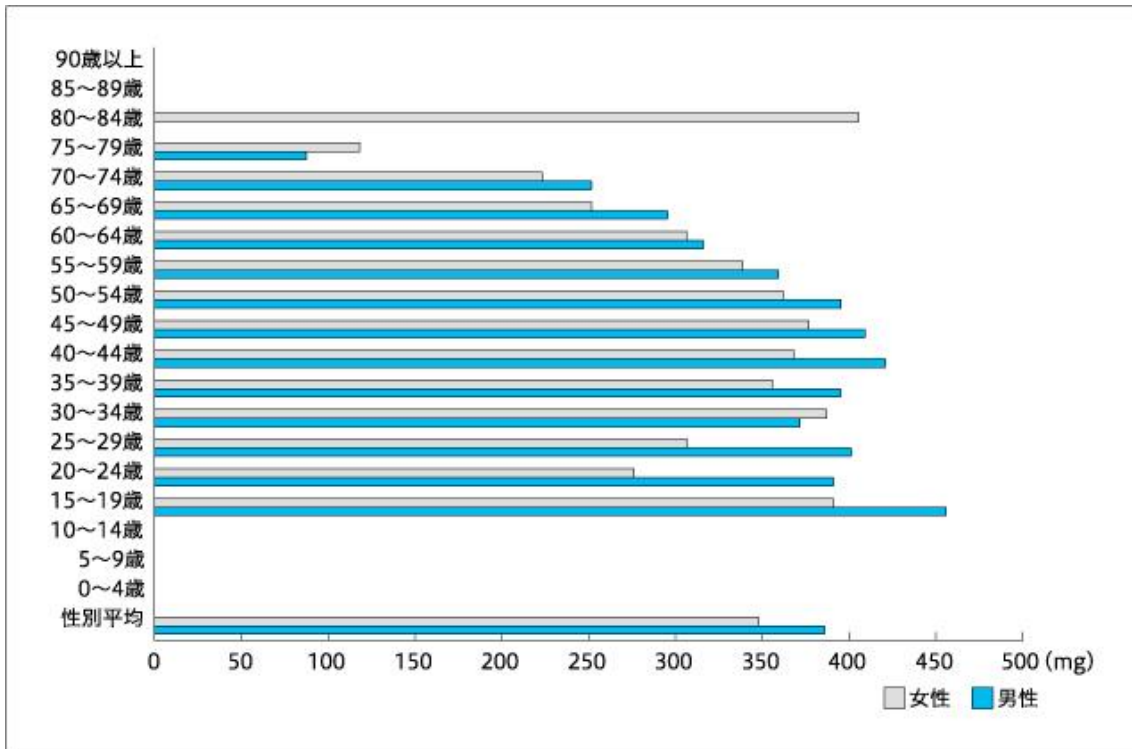


図7 2018年度CLZ使用入院患者平均投与量(性・年齢階級別)

Figure 7: The mean dosage for hospitalized patients using CLZ in FY 2018, by sex and age group