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Financial conflicts of interest among authors of clinical practice guideline for headache disorders in Japan

Anju Murayama[1*] and Yuki Senoo[2]

Abstract

Background Financial relationships between clinical guideline authors and pharmaceutical companies introduce conflicts of interest (COI), potentially biasing guideline recommendations. Thus, proper management of COI is paramount for clinical guideline authors. Nevertheless, little is known about COI among neurology clinical guideline authors. This study aimed to evaluate the financial relationships between pharmaceutical companies and authors of Clinical Practice Guideline for Headache Disorders (CPGHD) in Japan.

Methods This is a retrospective analysis of 2016–2020 personal payments data disclosed by all pharmaceutical companies affiliated with the Japan Pharmaceutical Manufacturers Association. We examined amounts and fraction of personal payments to all 57 CPGHD authors and all neurologists board-certified by the Japanese Society of Neurology. Payment data was descriptively analyzed at individual author level.

Results Among 57 CPGHD authors, 56 (98.3%) received personal payments totaling $2.7 million from pharmaceutical companies between 2016 and 2020. Median five-year payments were $89,955 for CPGHD authors, while $521 for board-certified neurologists. The CPGHD chairperson and vice chairperson received substantial payments during the guideline development period. Nevertheless, because of less rigorous and transparent COI policy compared to international standard policies, only 10 authors disclosed their financial relationships with the pharmaceutical companies in the guideline.

Conclusions More than 98% of CPGHD authors received much higher personal payments from pharmaceutical companies than those to board-certified neurologists during the guideline development period in Japan.

Keywords Conflicts of interest, Clinical practice guideline, Health policy, Evidence-based medicine, Ethics

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Introduction

Clinical practice guidelines (CPGs) are instrumental in standardizing diagnostic and treatment protocols based on the best available evidence and a tool to endorse evidence-based medicine in clinical practice [1, 2]. However, the credibility of these guidelines is often at risk due to potential conflicts of interest (COIs) among CPG developers. Over recent years, there has been a growing focus on the financial relationships between CPG developers and the healthcare industry, both within Japan and globally [3–9]. While not all financial interactions could lead to problematic relationships and harmful influence on patients, some can introduce bias into CPG recommendations, potentially endangering patient-centered care [2, 10, 11]. To mitigate this concern, many national and international professional organizations have implemented strict COI management policies [1, 2, 5, 11–14]. Given the far-reaching impact of CPGs on patients, clinicians, and other stakeholders, stringent COI management—including full disclosure, minimization of COIs among authors and organizations, and appointment of COI-free chairs for CPGs—is essential for creating reliable guidelines and advancing patient-centric care in the field of neurology and beyond [2, 11, 15, 16].

Recent years have seen the introduction of expensive new medications for headache management, contributing to rising healthcare costs. Previous studies have shown that the majority of neurologists in the United States (US) have received personal payments from pharmaceutical companies [15, 17, 18]. Additionally, there are remarkable development and introduction of novel headache drugs targeting anti-calcitonin gene-related peptide (CGRP) and its receptors such as atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, and ubrogepant, which significantly increased healthcare costs in the US [19]. Of these novel drugs, galcanezumab (Empality manufactured by Eli Lilly Japan and marketed by Daiichi Sankyo), fremanezumab (Ajovy manufactured by Otuka Pharmaceuticals), and erenumab (Aimovig manufactured by Amgen) were approved in Japan in 2021. In this context, it becomes even more critical for authors of CPGs in headache management in Japan to manage and disclose their financial relationships with the pharmaceutical companies transparently and accurately. Despite the growing concern over this issue, there is a notable lack of research exploring these financial relationships in the field of neurology in Japan. The present study aims to address this gap by investigating the nature and prevalence of financial ties between pharmaceutical companies and CPG authors in the field of headache management in Japan, using publicly disclosed payments data.

Methods

Study setting & participants

This cross-sectional retrospective study examined size and prevalence of personal payments made by pharmaceutical companies to all authors for Japanese Clinical Practice Guideline for Headache Disorders 2021 (CPGHD) developed by the Japanese Society of Neurology, Japanese Headache Society, and Japanese Society of Neurological Therapeutics in 2021 [20]. We considered all personal payments for lectures, consultancy services, and writing manuscript and pamphlet from pharmaceutical companies affiliated with the Japan Pharmaceutical Manufacturers Association between 2016 and 2020. Additionally, to compare the size of personal payments to the CPGHD authors with general neurologists in Japan, we also included all neurologists board certified by the Japanese Society of Neurology, the sole professional medical society which issue board-certification of neurologists in Japan.

Data collection & payment source

We collected all CPGHD authors' names and their affiliations from the CPGHD main text and all names of board-certified neurologists from the webpage of the Japanese Society of Neurology as of 2022, as performed in previous studies [21, 22]. As previous research explained [23], all pharmaceutical companies which affiliate with the Japan Pharmaceutical Manufacturers Association are demanded to disclose their payments concerning lectures, consultancy services, and writing manuscript and pamphlet to physicians with the individual physician names who received the payments. However, the companies update their payment data annually and remove data from previous years. An independent research group voluntarily collects all payments data from the pharmaceutical companies from 2016, and payments in the year of 2016 were the oldest data available from the disclosed public data. Therefore, payments data from 2016 to 2019 were extracted from a publicly accessible payment database [24]. Payments to the CPGHD authors in 2020 were collected directly from each affiliated pharmaceutical company's webpage.

Data analysis

We calculated the total amounts of payments and number of CPGHD authors and neurologists receiving payments. Descriptive analyses including mean, standard deviation (SD), median, and interquartile range (IQR) were performed on payment data collected from the companies between 2017 and 2020. Additionally, the payments were analyzed by payment category and companies making the payments. Differences in the proportion of physicians receiving payments and mean payment amounts between the CPGHD authors and board-certified neurologists

were evaluated by chi-square test and Mann-Whitney U test, as the payment distribution was highly skewed. Payment values were converted from Japanese yen to U.S. dollars using the 2020 average monthly exchange rates of 106.8 yen per $1. Data extraction and analyses were performed with Python 3.9.12 (Python Software Foundation, Beaverton, OR, USA), Microsoft Excel, version 16.0 (Microsoft Corp., Redmond, WA, USA), and Stata version 17.0 (StataCorp, College Station, TX, USA).

Ethical clearance

As this study was a retrospective analysis of publicly available data and met the definition of non-human subjects research, no institutional board review and approval were required in accordance with the Japanese Ministry of Health, Labor, and Welfare and Ministry of Education,, Culture, Sports, Science and Technology's Ethical Guidelines for Medical and Health Research Involving Human Subjects [25]. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Payments to the authors of clinical practice guideline for headache disorders 2021

Of a total of 57 CPGHD authors, 56 (98.3%) received at least one personal payment from the pharmaceutical companies over the five years. The total amounts of personal payments were $2,745,739 entailing 3,155 in the number of payments over the five years. The median and mean personal payments per author were $15,312 (IQR: $5,889–$45,503) and $48,171 (SD: $83,524) for the five-year period, respectively (Table 1). Of all JCPGH authors, 64.9% and 15.8% received more than $10,000 and $100,000 personal payments. One author received $346,714 over the five years, the largest amounts among the CPGHD authors. The chair and vice chairperson received a total of $42,887 and $157,998 in personal compensations for lecturing, consulting, and writing manuscript from the pharmaceutical companies during the five years prior to the CPG publication, respectively.

Regarding yearly breakdown of personal payments, there were no general trends in the number of authors receiving payments and mean payment amounts between 2016 and 2020 (Table 1). Although more than 80% of authors received one or more personal payments each year, one-fifth of authors annually received more than $10,000. Both of the chairperson and vice chairperson received personal payments every year between 2016 and 2020. When we limited the payments for the past three years between 2018 and 2020, 93.0% (53 out of 57) of the CPGHD authors received one or more personal payments from the pharmaceutical companies. The authors received $8,374 (IQR: $3,161–$20,505) per author in the median three-year combined total amounts.

Payments by pharmaceutical company and payment category

Of 55 pharmaceutical companies making payments to the CPGHD authors (Table 2), Daiichi Sankyo made the largest amounts ($404,205) of personal payments to the JCPGH authors over the five years, followed by Pfizer Japan ($362,225), Eisai ($288,098), Otsuka Pharmaceutical ($242,964), and Eli Lilly Japan ($193,491). These five companies accounted for 54.3% ($1.5 million) of total personal payments to the JCPGH authors. Of these payments, lecturing compensation payments accounted for 79.2% ($2.2 million) of the total amounts.

Table 1 Summary of personal payments from pharmaceutical companies to the authors of Japanese Clinical Practice Guideline for Headache Disorders 2021

Variables	2016	2017	2018	2019	2020	Total amounts
Total amount of payments, $	507,701	620,872	591,227	524,793	501,146	2,745,739
Mean payments per author (standard deviation), $	8,907 (16,223)	10,892 (19,940)	10,372 (20,497)	9,207 (16,638)	8,792 (15,115)	48,171 (83,524)
Median payments per author (interquartile range), $	3,087 (626–7,767)	3,417 (751–10,277)	2,294 (521–6,465)	2,859 (743–6,306)	3,186 (551–7,981)	15,312 (5,889 – 45,503)
Maximum, $	86,433	95,189	87,701	81,772	69,892	346,714
Authors with payments (*N* = 57), n (%)						
Any payments	51 (89.5)	51 (89.5)	46 (80.7)	48 (84.2)	47 (82.5)	56 (98.3)
>$10,000	12 (21.1)	15 (26.3)	11 (19.3)	11 (19.3)	11 (19.3)	37 (64.9)
>$50,000	2 (3.5)	4 (7.0)	3 (5.3)	2 (3.5)	2 (3.5)	13 (22.8)
>$100,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (15.8)
>$250,000	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (5.3)

Japanese yen (¥) were converted to US dollars ($) using the 2020 average monthly exchange rate of ¥106.8 per $1

Table 2 Personal payments by company and payment category

Variables	Payment amounts (%), $
Total amounts of payments	2,745,739 (100)
Top 5 companies making the largest payment amounts	
Daiichi Sankyo	404,205 (14.7)
Pfizer Japan	362,225 (13.2)
Eisai	288,098 (10.5)
Otsuka Pharmaceutical	242,964 (8.8)
Eli Lilly Japan	193,491 (7.0)
Payment categories	
Lecturing payments	2,173,374 (79.2)
Consulting payments	433,238 (15.8)
Writing payments	139,128 (5.1)

Table 3 Personal payments to the authors of Japanese Clinical Practice Guideline for Headache Disorders 2021 and board-certified neurologists from the pharmaceutical companies between 2016 and 2020

Variables	Authors of Clinical Practice Guideline for Headache Disorders 2021 (*N* = 57)	Board-certified neurologists (*N* = 6,107)
Total amounts of payments, $	2,745,739	45,726,920
Number of authors/neurologists receiving payments, n (%)	56 (98.3)	3,615 (59.2)
Payments per author/neurologist, $		
Median (interquartile range)	15,312 (5,889–45,503)	521 (0–3,556)
Mean (standard deviation)	48,171 (83,524)	7,488 (27,644)
Maximum	346,714	616,257
Number of authors/neurologists receiving payments by year, n (%)		
2016	51 (89.5)	2,179 (35.7)
2017	51 (89.5)	2,242 (36.7)
2018	46 (80.7)	2,245 (36.8)
2019	48 (84.2)	2,292 (37.5)
2020	47 (82.5)	2,017 (33.0)

Payments to board-certified neurologists in Japan

Of 6,107 neurologists who were board-certified by the Japanese Society of Neurology as of 2022, 3615 (59.2%) received one or more personal payments over the five years (Table 3). The total amounts of personal payments to all board-certified neurologists were $45,726,920 for the five-year period. Mean and median personal payments per neurologist were $7,488 (SD: $27,644) and $521 (IQR: $0–$3,556). The JCPGH authors were significantly more likely to receive personal payments from the pharmaceutical companies (98.3% vs. 59.2%, $p<0.001$ in chi-square test) and the mean payments were significantly higher in JCPGH authors than those to board-certified neurologists ($48,171 vs. $521. $p<0.001$ in Mann-Whitney U test).

Self-declared COIs and COI policy for authors

Of the 57 authors, only 10 (17.5%) disclosed their financial relationships with pharmaceutical companies, specifically regarding payments received for lecturing, consulting, and writing over the past three years. Consequently, the financial relationships between pharmaceutical companies and at least 43 other authors who received personal payments between 2018 and 2020 were not disclosed in the CPGHD.

Furthermore, the Japanese Society of Neurology's COI policy mandates that CPGHD authors disclose only those financial relationships with pharmaceutical and medical device companies that exceed certain thresholds (e.g., more than 500,000 Japanese yen, equivalent to $4,682, per company per year per activity for lecturing, consulting, and writing payments). The policy also stipulates that experts receiving payments exceeding a certain threshold (e.g., more than 1,000,000 Japanese yen, equivalent to $9,365, per company per year per activity) should not serve as CPG chairpersons. Among the 14 CPGHD authors who received payments exceeding these thresholds for lecturing, consulting, and writing for the past three years (2018–2020), 6 (42.9%) did not disclose their financial COIs in the CPGHD.

The COI policy obliges CPG authors to disclose financial relationships between the professional medical societies responsible for developing the CPG and any companies. Despite that Eli Lilly, the manufacturer of galcanezumab in Japan, sponsored and distributes video lectures of CPGHD to patients and physicians on the company webpage [26], no such disclosure statements regarding financial relationships between pharmaceutical companies and the three professional medical societies that developed the CPGHD were present [20].

Discussion

This study represents the comprehensive examination of the prevalence and magnitude of financial conflicts of interest among authors of the Japanese Clinical Practice Guideline for Headache Disorders 2021. The guideline was jointly published by the Japanese Society of Neurology, the Japanese Headache Society, and the Japanese Society of Neurological Therapeutics. Our findings reveal that over 98% and 93% of CPGHD authors received personal payments from pharmaceutical companies the five and three years before the CPGHD publication, respectively. Notably, the majority of these payments originated from pharmaceutical companies that manufacture and market novel CGRP monoclonal antibodies, such as Daiichi Sankyo, Otsuka Pharmaceuticals, and Eli Lilly. Both the chairman and vice chairman of the guideline

committee had substantial financial relationships with these companies for purposes unrelated to research. Furthermore, the payments received by CPGHD authors were significantly larger than those received by general board-certified neurologists in Japan. Despite these extensive financial ties, the relationships were not fully disclosed in the CPGHD, largely due to the unreasonably high thresholds set for financial disclosure. Collectively, these findings raise significant scientific and ethical concerns regarding the financial relationships between CPG authors and pharmaceutical companies in the field of neurology in Japan.

First, this study demonstrated that nearly all CPGHD authors had financial ties to the pharmaceutical companies during the CPG development period. In contrast to this high prevalence of COIs among CPGHD authors, studies in the US and other developed countries report lower rates. Using a legal-binding payment database, Combs et al. found that 53% of gastroenterology CPG authors received personal and/or research payments from pharmaceutical and medical device companies in the US in 2018 [27]. Similarly, Carlisle et al. reported that 59.3% of urology CPG authors received personal and/or research payments in the US in 2018 [28]. One recent study showed that 48.0% of American Diabetes Association CPG authors had financial relationships with the healthcare industry [29]. Elder et al. found that 56% of Canadian CPG authors had financial COIs with the healthcare industry in 2020 [30].

These lower COIs among CPG authors in the US could be attributed to recent developments of increased transparency initiatives and stricter COI policies. Indeed, research has indicated a decline in non-research payments to physicians in the US, while a smaller proportion of physicians have increasingly had stronger financial interactions with industry since the inception of the US transparency database in 2014 [32–35]. The US federal agencies have strengthened their investigations into scrutiny of physician-industry financial relationships and the accurate reporting of payments made by the industry to physicians [36–42].

Meanwhile, the high proportion of CPG authors receiving personal payments is consistent with previous research conducted in Japan where the importance of transparency and proper management of COIs was undervalued [3–7, 43–50]. Furthermore, the CPGHD chairpersons had strong financial ties to the pharmaceutical companies. Previous research has reported that the proportion of CPG authors receiving personal payments in Japan was 74–92% in oncology [44, 50, 51], 86.4–94.4% in cardiology [52, 53], 87.0–91.9% in infectious diseases [42, 54], 88% in nephrology [5], 88.2–100% in gastroenterology [3, 6, 44], 88.6% in urology [46], 90.6% in dermatology [45], 91.3–100% in rheumatology [4, 49], 93.1–96.3% in otolaryngology [47, 55], and 94.6% in hematology [7].

These high prevalence of financial COIs among CPG authors and strong financial ties of CPGHD chairpersons with the pharmaceutical companies in Japan are clear violations from global-standard COI policies. For instance, the U.S. National Academy of Medicine 2011 report "Clinical Practice Guidelines We Can Trust", previously known as Institute of Medicine, strongly recommends that less than half of a CPG development group should have financial COIs with industry [2]. Similarly, the Guidelines International Network also advocates that ideally, no panel members should have COIs, and at most, they should limit a minority of CPG authors with financial COIs with industry [1]. The 98.3% prevalence of COIs in this study is not just a minor deviation but a complete departure from these established international standards, raising concerns about the impartiality and credibility of the guidelines.

Nevertheless, only 17.5% of CPGHD authors disclosed their financial relationships with pharmaceutical companies. This significant under-disclosure could be attributed to the unreasonably high thresholds for COI declaration set by the Japanese Society of Neurology, which mandates disclosure only for payments exceeding $4,682 per year per company for activities such as lecturing, consulting, and writing. As a result, the majority of personal payments to CPGHD authors remain undisclosed, thereby concealing potential financial COIs for both CPGHD readers and the general public. A 2018 literature review by the U.S. Preventive Services Task Force found that most COI policies from international and U.S. medical societies require CPG authors to disclose all financial relationships, regardless of the payment amount [13].

Additionally, the mean personal payments to CPGHD authors were more than 6.4 times larger than those received by board-certified neurologists in Japan. While CPG authors often have extensive clinical and research experience and may hold authoritative positions of authority such as university professorships or hospital directorships [54, 56], their close financial ties to the industry raise concerns. Although such financial interactions can be beneficial to patient care and innovation in healthcare [57], it is essential to maintain a balanced composition of authors to ensure the trustworthiness of CPGs and recommendations. While input from experts with industry ties can be valuable, it is of equal importance to minimize the industry influence on CPG recommendations. In accordance with these principles, both the U.S. National Academy of Medicine and the Guidelines International Network recommend that at least half of CPG authors should be free from any financial COIs with industry. Some professional medical societies, such as the American Urological Association, mandate that

CPG authors refrain from receiving any form of compensation or consulting payments from industry both during and for one year following CPG development [1, 2, 5, 12, 58].

Policy recommendations

In light of these findings, this study underscores the urgent need for enhanced COI management strategies among CPGHD authors in Japan. In this article, we propose several recommendations for enhancing the quality of CPGHDs and COI management strategies.

First, CPGHD authors should disclose all financial relationships, regardless of the monetary value. This is particularly crucial in the context of personal payments to authors for lecturing, consulting, and writing fees, which constituted the primary focus of our evaluation. To ensure full transparency, the Japanese Society of Neurology must revise its existing COI policy, which currently mandates the declaration and disclosure of only $4,682 per year per company per activity. The society must adopt more rigorous and transparent COI policies in accordance with the recommendations set forth by the U.S. National Academy of Medicine and the Guidelines International Network. Second, the society should appoint experts who do not have financial conflicts of interest to serve as a minimum of half of the CPG authors, as recommended by international CPG development organizations. Third, even if the society establishes CPG development groups comprising authors who have financial COIs, the CPGHD authors should refrain from accepting personal payments from pharmaceutical companies that could potentially benefit from CPG recommendations. They should also avoid participating in industry-sponsored promotional events during the CPG development period. Fourth, the society should establish an independent group with the responsibility of monitoring and evaluating the accuracy and content of COIs declared by CPG authors.

Concurrently, there is a concern that these more rigorous COI policies may preclude the involvement of experts with substantial research and clinical experience, who also have financial interactions with healthcare companies, in CPG development. The potential consequence of this is a reduction in the quality of CPG recommendations and contents. However, the current global-standard COI policies permit up to half of CPG authors to have financial COIs with industry, thereby facilitating valuable input from the experts who collaborate with industry [11].

In addition to aforementioned recommendations for CPG authors and development organizations, we also recommend that the Japanese government create a publicly accessible transparency database that discloses all research and non-research payments from pharmaceutical and medical device companies to healthcare professionals and organizations, similar to the US Open Payments Database. At present, most pharmaceutical companies voluntarily disclose payments to physicians, including individual names, for specific categories such as lecturing, consulting, and writing fees, in accordance with guidance from the Japan Pharmaceutical Manufacturers Association. However, these data are only available on individual company webpages, and the format is not readily accessible to the public. Despite the efforts of an independent research group to collect and publish an online database of these payments, the database is not updated in a timely manner due to constraints in human and financial resources, and it may encompass inaccuracies. Moreover, in contrast to transparency databases in other developed countries, such as the US Open Payments Database, the Disclosure UK database, and the Medicines Australia database, the Japanese database does not provide the option to directly download payment records. This presents an additional major obstacle to researchers and media in Japan seeking to access research related to COI and physician-industry relationships.

It is our contention that the establishment of a government-operated transparency database would serve to provide the public, patients, physicians, researchers, and other stakeholders with a reliable source of information. This would, in turn, facilitate increased scrutiny of physician-industry financial relationships and their impact on patient care, healthcare expenditures, and the national healthcare system in Japan. Since the inception of the US Open Payments Database in 2014, there has been a notable increase in research and public scrutiny related to COIs and their influence on various aspects of healthcare. A recent systematic review has demonstrated that payments from pharmaceutical companies to physicians are significantly associated with higher prescribing volumes and healthcare costs [59]. Of the 36 articles included in the review, 35 (97.2%) were conducted in the US, and 34 (94.4%) utilized the Open Payments Database to examine the relationship between payments and prescribing patterns [59]. Another systematic review examined the accuracy of self-declared COIs among CPG authors, with 30 (75.0%) of the 40 studies included in the review using the Open Payments Database to assess COI accuracy [60]. In response to the increased use of transparency databases and the heightened scrutiny of physician-industry financial relationships in the US, numerous professional medical societies, teaching hospitals, and universities have utilized these databases to validate the accuracy of financial COIs declared by CPG authors, research article authors, physician researchers, and clinicians [4, 61].

Limitations

This study has several limitations. First, the focus on a single set of CPG may limit the generalizability of our findings to other medical fields or countries. Second, the payment data were sourced from a secondary database maintained by an independent research group. While this database includes nearly all personal payment data gathered from pharmaceutical companies affiliated with the Japan Pharmaceutical Manufacturers Association between 2016 and 2019, there are no legal requirements in Japan that mandates the accurate disclosure of such payments to physicians [23, 62]. Therefore, the study cannot rule out the possibility of errors and misreporting in the disclosed payment data. Finally, as the payment data were voluntarily disclosed by companies affiliated with the Japan Pharmaceutical Manufacturers Association, financial relationships between CPGHD authors and undisclosed pharmaceutical companies may exist but remain unreported. It is worth noting, however, that all pharmaceutical companies manufacturing CGRP monoclonal antibodies in Japan have disclosed their payment data, and this study incorporates that information. As a result, this study is able to assess the scope and prevalence of financial relationships between CPGHD authors and major pharmaceutical companies in Japan. The likelihood of significant financial relationships with undisclosed companies is minimal in the context of this study.

Conclusions

Nearly all the authors of the Japanese Clinical Practice Guideline for Headache Disorders developed by the Japanese Society of Neurology, Japanese Headache Society, and Japanese Society of Neurological Therapeutics received personal payments from pharmaceutical companies during the CPG development period. These findings call for immediate policy interventions to enhance the transparency, integrity, and reliability of clinical practice guidelines for headache disorders in Japan.

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Author contributions

A.M. and Y.S. contributed to conceptualization; methodology; resource; investigation; writing - original draft; writing - review & editing. In addition, A.M also contributed to the formal analysis; visualization; study administration of the study.

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Data availability

All data used in this study is available from Yen For Docs database run by Medical Governance Research Institute (https://yenfordocs.jp/) and each pharmaceutical companies belonging to the Japan Pharmaceutical Manufacturers Association. Due to the privacy protection, the datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

As this study was a retrospective analysis of publicly available data and met the definition of non-human subjects research, no institutional board review and approval were required in Japan. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Patient consent statement

Not applicable.

Permission to reproduce material from other sources

Not applicable.

Clinical trial registration

Not applicable.

Generative AI in scientific writing

During the preparation of this work, the authors used ChatGPT version 4.0 to check and correct grammatical and spelling errors. After using this tool, the authors carefully reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Competing interests

The authors declare no competing interests.

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