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## Financial conflicts of interest in clinical practice guidelines for bipolar disorder and major depressive disorder in Japan

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**Title: Financial conflicts of interest in clinical practice guidelines for bipolar disorder and major depressive disorder in Japan**

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Conflicts of interest, pharmaceutical companies, clinical practice guideline, health policy, evidence-based medicine, ethics, depression, bipolar disorder

**Author contribution:**

A.M. contributed to data collection, resource, software, formal analysis, visualization, supervision, and study administration. All authors (A.M., H.K., and Y.S.) contributed to study conceptualization, methodology, writing the original draft, and reviewing the draft.

**Abstract**

**Objective**

Clinical practice guidelines (CPGs) are essential for standardizing patient care based on evidence-based medicine. However, the presence of financial conflicts of interest (COIs) among CPG authors can undermine their credibility. This study aimed to examine the extent and size of COIs among authors of psychiatry CPGs in Japan.

**Methods**

This cross-sectional analysis of disclosed payments from pharmaceutical companies assesses the prevalence and magnitude of personal payments for lecturing, consulting, and writing to CPGs for bipolar disorder and major depressive disorder in Japan between 2016 and 2020.

**Results**

This study found that 93.5% of authors received payments over a five-year period, with total payments exceeding \$4 million. The median payment per author was \$49,422 (interquartile range: \$7,792 – \$111,567), with a notable concentration of payments among a small number of authors, including the CPG chairperson. Despite these extensive financial relationships, only a fraction of authors disclosed their COIs in the CPGs. These large amounts of personal payments were made by pharmaceutical companies manufacturing new antidepressants and sleeping aids listed in the CPGs.

**Conclusions**

This study found that more than 93% of authors of Japanese major depressive disorder and bipolar disorder CPGs received considerable amounts of personal payments from the pharmaceutical industry. The findings highlight deviations from international COI management standards and suggest a need for more stringent COI policies for psychiatry CPGs in Japan.

## Introduction

Clinical practice guidelines (CPGs) have been increasingly used as a tool to endorse evidence-based medicine for healthcare professionals in their clinical practice<sup>1 2</sup>. CPGs are developed based on the best available evidence and include recommendations for diagnosis and treatment of specific diseases. Nevertheless, the integrity and recommendations of CPGs are frequently compromised by conflicts of interest (COIs) between the guideline authors and the pharmaceutical industry, spanning various medical specialties. In the field of psychiatry, there is substantial documentation of ghostwriting by pharmaceutical industry<sup>3</sup> and widespread financial COIs between CPG authors and pharmaceutical companies<sup>4-7</sup>. Furthermore, studies showed that financial COIs are associated with a propensity for CPGs to make recommendations favorable to the healthcare industry<sup>4 8</sup>. This underscores the necessity for rigorous management of financial COIs among CPG authors, particularly in psychiatry<sup>6 9 10</sup>. A recent study demonstrated that 60% of panel members of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), fifth edition, text revision published by the American Psychiatry Association in 2022 received payments from the pharmaceutical industry<sup>11</sup>. As the DSM-5 is widely used as a standard for psychiatric disorders' definitions and symptom criteria, influencing treatment selection and approval of new drugs worldwide<sup>11</sup>, the widespread financial COIs among the DSM-5 panel members are concerning. However, financial COIs among psychiatry experts are not unique to international criteria and CPGs: they may also be problematic among authors of regional or national CPGs, as these guidelines include specific treatment recommendations that can influence the clinical practice of clinicians in each country or region.

To enhance the transparency of financial relationships between healthcare professionals and pharmaceutical companies, members of the Japan Pharmaceutical Manufacturers Association have voluntarily disclosed their financial interactions with healthcare professionals and organizations<sup>12</sup>. Subsequent research using this disclosed information has revealed that the vast majority of CPG authors in Japan received personal payments during the CPG development across various medical specialties<sup>12-22</sup>. However, the specifics of these financial relationships between pharmaceutical companies and Japanese CPG authors in psychiatry remain largely unexplored. Considering the patterns observed in previous studies, we hypothesized that financial COIs are widespread among psychiatry CPG authors in Japan.

## Methods

### *Study setting, participants, and data collection*

This cross-sectional analysis evaluated the extent and prevalence of financial interactions between pharmaceutical companies and authors of CPGs for major depressive disorder and bipolar disorder in Japan. The Japanese Society of Mood Disorders is responsible for the development of the sole CPGs for these conditions, namely Treatment Guideline I: Bipolar Disorder<sup>23</sup> and Treatment Guideline II: Major Depressive Disorder<sup>24</sup>. At the time of this study, the latest versions were published in June 2020 and July 2019, respectively.

The Japan Pharmaceutical Manufacturers Association, representing over 70 major

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6 113 pharmaceutical companies, mandates the disclosure of payments for lectures,  
7 114 consultancy, and writing to healthcare professionals, listing the recipients' names on  
8 115 company websites since 2013<sup>25-27</sup>. Despite annual updates and removal of previous  
9 116 years' data by these companies, the Medical Governance Research Institute has  
10 117 independently collected and disclosed this payment data on its public online database  
11 118 from 2016 to 2020, detailing individual physician and company contributions<sup>28</sup>. As the  
12 119 pharmaceutical companies have not individually disclosed other categories of non-  
13 120 research payments such as travel and accommodation fees, food and beverage fees, and  
14 121 royalties and ownership payments, this study incorporated all personal payments for  
15 122 lectures, consultancy, and writing from pharmaceutical companies to the psychiatry  
16 123 CPG authors from 2016 to 2020, following the approach of prior studies<sup>29-32</sup>.  
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19 125 *Data analysis*  
20 126 The study calculated the proportion of CPG authors receiving personal payments and  
21 127 assessed per-author payment amounts, including median, interquartile range, mean, and  
22 128 standard deviation. Payments were converted from Japanese yen to U.S. dollars using  
23 129 the 2020 average monthly exchange rate of 106.8 yen per \$1. Data extraction and  
24 130 analyses were executed using Python 3.9.12 (Python Software Foundation, Beaverton,  
25 131 OR, USA), Microsoft Excel, version 16.0 (Microsoft Corp., Redmond, WA, USA), and  
26 132 Stata version 17.0 (StataCorp, College Station, TX, USA).  
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29 134 *Use of large language model in the drafting*  
30 135 During the preparation of this work, the authors used ChatGPT version 4.0 to check and  
31 136 correct grammatical and spelling errors. After using this tool, the authors carefully  
32 137 reviewed and edited the content as needed and takes full responsibility for the content of  
33 138 the publication.  
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36 140 *Ethical clearance*  
37 141 As a retrospective analysis of publicly available data, this study was classified as non-  
38 142 human subjects research and did not require institutional review board approval in  
39 143 accordance with the Japanese Ministry of Health, Labor, and Welfare's Ethical  
40 144 Guidelines for Medical and Health Research Involving Human Subjects. The  
41 145 methodology adhered to the Strengthening the Reporting of Observational Studies in  
42 146 Epidemiology (STROBE) guideline.  
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45 148 *Patient and public involvement*  
46 149 No patients were involved in the preparation of this manuscript or the research project.  
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49 151 **Results**  
50 152 The study included 29 authors for the bipolar disorder CPG and 42 for the major  
51 153 depressive disorder CPG, with 25 individuals contributing to both. Consequently, 46  
52 154 unique CPG authors were analyzed (Table 1). Disclosure of financial COIs within the  
53 155 CPGs was self-reported solely by the writing authors. All authors (100%, 4 out of 4)  
54 156 associated with the bipolar disorder CPG and 85.7% (12 out of 14) with the major  
55 157 depressive disorder CPG declared financial COIs with pharmaceutical companies.  
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58 159 A significant majority, 43 authors (93.5%), received personal payments for lectures,  
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consulting, and writing from pharmaceutical companies between 2016 and 2020 (Table 2). The cumulative personal payments amounted to \$4,043,436 from 55 pharmaceutical companies over this period. The median payment per author was \$49,422 (IQR: \$7,792 – \$111,567), and the mean payment was \$87,901 (SD: \$111,270), indicating a skewed distribution where a few authors received disproportionately high payments. Notably, 15 authors (32.6%) received in excess of \$100,000 over five years. The chairperson of the guideline development committee received the highest total payment of \$506,108 for lecturing, consulting, and writing from pharmaceutical companies during this time. Payments for lecturing constituted \$2.7 million (65.8% of the total), with consulting and writing making up 25.8% (\$1.0 million) and 8.3% (\$337,255), respectively.

Annual analysis revealed a decline in total payments to CPG authors from \$959,503 in 2016 to \$697,170 in 2020 (Table 2). Correspondingly, the median annual payment per author decreased from \$11,865 (IQR: \$1,773 – \$24,498) in 2016 to \$2,693 (IQR: \$0 – \$22,968) in 2020. The proportion of authors receiving payments also fell from 91.3% in 2017 to 73.9% in 2020, yet a majority still received at least one personal payment annually.

Payments from the top 5 and 10 pharmaceutical companies constituted 53.3% (\$2.2 million) and 83.1% (\$3.4 million) of the total payments, respectively (Table 3). Sumitomo Pharma was the most generous, contributing \$695,031 (17.2%), followed by Eisai (10.1%, \$408,323), MSD (8.8%, \$357,526), Otsuka Pharmaceutical (8.8%, \$354,638), and Takeda Pharmaceutical (8.3%, \$337,370). Among these, MSD, Pfizer Japan, and Meiji Seika notably reduced their non-research payments from 2016 to 2020, whereas Eisai increased its payments from \$45,779 in 2016 to \$151,856 in 2020.

Table 4 presents the types of financial COIs self-reported by the CPG authors within each respective guideline. Among the six categories extracted from the CPG disclosures, compensation for lecturing was the most frequently declared (100% for the bipolar disorder CPG and 78.6% for the major depressive disorder CPG). This was followed by scholarship donations and participation in pharmaceutical company advisory boards. The lack of a specified declaration period precluded the assessment of the accuracy of each CPG author's self-reported COI status against the payment data released by the pharmaceutical companies.

## Discussion

This cross-sectional analysis of publicly disclosed payment data from pharmaceutical companies provides a detailed examination of the extent and prevalence of financial COIs among authors of the Japanese Society of Mood Disorders' Treatment Guideline I: Bipolar Disorder<sup>23</sup> and Treatment Guideline II: Major Depressive Disorder<sup>24</sup>. These CPGs are considered by physicians the authoritative and trustworthy sources for the treatment of bipolar disorder and major depressive disorder in Japan<sup>33</sup>. To the best of our knowledge, this is the first in-depth study to analyze the financial relationships between psychiatry CPG authors and pharmaceutical companies in Japan using disclosed payment data. The findings reveal that a significant majority (93.5%) of CPG authors received personal payments for lecturing, consulting, and writing, with a total sum of \$4.0 million between 2016 and 2020. The median payment per author was



\$49,422, with a minority, including the CPG chairperson, receiving substantial sums. Nearly all authors involved in writing the CPGs self-reported financial COIs with pharmaceutical companies. Notably, the bulk of personal payments to CPG authors came from companies that manufacture antidepressants and sleeping pills in Japan. However, other CPG authors did not publicly disclose their financial COIs with these companies. When compared to previous studies and international COI policies for CPG authors, these findings raise concerns for physicians, patients, policymakers, and other stakeholders within and beyond Japan.

The study highlights that over 93% of the authors of CPGs for bipolar disorder and major depressive disorder had financial relationships with pharmaceutical companies. Given the publication dates of the CPGs between 2019 and 2020, these financial relationships likely occurred during the development of the CPGs. This high percentage of authors receiving personal payments aligns with findings from other specialties within Japan<sup>12-15 17-22 34-37</sup>, where the proportion of CPG authors with personal payments ranged from 86.4% in cardiology<sup>38</sup> to 94.6% in hematology<sup>14</sup>.

In contrast, research from other developed countries, such as the United States, reports lower proportions of CPG authors with financial COIs. For instance, 67% of authors for the DSM-5 mood disorders section disclosed financial COIs with the healthcare industry<sup>9</sup>. Additionally, a study by Cosgrove et al. found that only 18% of major depressive disorder CPG authors across eight countries had financial COIs with pharmaceutical companies<sup>4 10</sup>. In Canada, half of the authors of the CPG for depressive disorder developed by the Canadian Network for Mood and Anxiety Treatments reported financial COIs with the healthcare industry<sup>39</sup>. Other specialties in the United States also showed lower percentages, with 53% of gastroenterology CPG authors<sup>40</sup> and 59.3% of urology CPG authors receiving personal and/or research payments<sup>41</sup>. Moreover, Mooghali et al. reported that 73.7% of physician CPG authors in the United States received personal and/or research payments from healthcare companies<sup>42</sup>.

Furthermore, this investigation revealed that a select group of CPG authors, including the chairperson, received substantial personal payments from pharmaceutical companies. Only authors involved in writing the CPGs were mandated to declare their financial COIs, while other contributors did not publicly disclose any financial COIs with these companies. These results indicate that authors of Japanese CPGs for bipolar disorder and major depressive disorder clearly violate international COI policies on CPG development in several respects. The U.S. National Academy of Medicine's 2011 report and the Guidelines International Network advocate for a majority of CPG authors to be free from financial COIs<sup>1 2</sup>. These policies also stipulate that the chairperson of CPG development should not hold any COIs<sup>1 2</sup>. The Guideline Panel Review Working Group's criteria for red flags, as published in the British Medical Journal in 2013, indicate that financial COIs held by a CPG chairperson and multiple authors are significant concerns for the trustworthiness of the CPGs<sup>43</sup>. The prevalence of COIs exceeding 93% in this study is not a marginal discrepancy but a significant deviation from these standards, casting doubt on the objectivity and reliability of the guidelines.

Moreover, the study uncovered that substantial payments were made by pharmaceutical

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companies marketing new antidepressants and sleep aids in Japan. For example, Sumitomo Pharma, the top paying company, manufactures lurasidone (brand name: Latuda), approved for bipolar disorder and schizophrenia in 2020, and co-promotes venlafaxine hydrochloride (brand name: Effexor) with Pfizer Japan since 2018. MSD, another major payer, produces suvorexant (brand name: Belsomra), the world's first orexin receptor antagonist. Otsuka Pharmaceutical is noted for one of the major manufacturers of atypical antipsychotic medications such as aripiprazole (brand name: Abilify) and brexpiprazole (brand name: Rexulti) which are the most widely prescribed atypical antipsychotic drugs in Japan<sup>44</sup>. Despite these financial ties between the CPG authors and the pharmaceutical companies, the Japanese Society of Mood Disorders actively endorses adherence to these CPGs<sup>45 46</sup>. Considering that the CPGs for bipolar disorder and major depressive disorder include pharmacotherapy recommendations involving drugs from these companies, it is imperative to address the close financial relationships between CPG authors and the pharmaceutical industry. We strongly recommend the Japanese Society of Mood Disorders to enforce more transparent and stringent COI management strategies in the CPG development process for bipolar disorder and major depressive disorder, ensuring the integrity and credibility of these guidelines.

### *Limitations*

This study is subject to several limitations. Primarily, the study focus on CPGs for bipolar disorder and major depressive disorder in Japan would limit the generalizability of our findings to other medical fields or countries. Additionally, the payment data were derived from a secondary source, the Medical Governance Research Institute's database, which contains payment information from member companies of the Japan Pharmaceutical Manufacturers Association for the period 2016-2020<sup>26 47</sup>. Absent legal mandates for precise payment disclosures in Japan, the potential for inaccuracies or underreporting in the database cannot be discounted. Furthermore, the voluntary nature of these disclosures means that financial interactions between CPG authors and non-disclosing pharmaceutical entities may remain undetected. Nevertheless, given that the member companies account for 80% of the market share for drugs and medical products in Japan<sup>48</sup>, the impact of financial relationships between the CPG authors and uncovered companies would be minimized.

### *Conclusions*

More than 93% of the authors of the Treatment Guidelines for Bipolar Disorder and Major Depressive Disorder developed by the Japanese Society of Mood Disorders received personal payments for the reimbursement of their lecturing, consulting, and writing activities from the pharmaceutical companies manufacturing related drugs. The total amounts of personal payments to the CPG authors were more than \$4.0 million over the five years. Nevertheless, the financial COIs were only declared by the limited group of CPG authors. Further transparent and rigorous COI management strategies must be warranted in the Japanese Society of Mood Disorders.

### **Conflicts of interest:**

The authors declare that there were no conflicts of interest for this study.

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**IRB Statement**

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’s Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

**Declaration of 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.

**Data availability statement:**

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 privacy protection, payment data of individual CPG authors will be available from the corresponding author upon reasonable request.

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Table 1. Demographic characteristics of clinical practice guideline authors for bipolar disorder and major depressive disorder

| Variables                                                                      | Guideline disease category |                           | Overall        |
|--------------------------------------------------------------------------------|----------------------------|---------------------------|----------------|
|                                                                                | Bipolar disorder           | Major depressive disorder |                |
| Number of authors                                                              | 29                         | 42                        | 46             |
| Role of guideline authors                                                      |                            |                           |                |
| Writing authors                                                                | 4 (13.8)                   | 14 (33.3)                 | Not calculated |
| Supporting authors                                                             | 5 (17.2)                   | 11 (26.2)                 | Not calculated |
| Guideline development committee authors                                        | 20 (69.0)                  | 17 (40.5)                 | Not calculated |
| Number of authors with self-declared conflicts of interest, n (%) <sup>a</sup> | 4 (100)                    | 12 (85.7)                 | Not calculated |

<sup>a</sup> Conflicts of interest were only declared by writing authors.

Table 2. Summary of personal payments from pharmaceutical companies to psychiatry clinical practice guideline authors between 2016 and 2020

| Variables                                            | 2016                    | 2017                    | 2018                | 2019                 | 2020               | Total amounts            |
|------------------------------------------------------|-------------------------|-------------------------|---------------------|----------------------|--------------------|--------------------------|
| Total amount of payments, \$                         | 959,503                 | 873,288                 | 769,649             | 743,826              | 297,170            | 4,043,436                |
| Mean payments per author (standard deviation), \$    | 20,859 (27,155)         | 18,985 (24,259)         | 16,732 (24,649)     | 16,170 (21,256)      | 15,156 (22,221)    | 87,901 (111,270)         |
| Median payments per author (interquartile range), \$ | 11,865 (1,773 – 24,498) | 10,239 (1,517 – 25,058) | 2,294 (521 – 6,465) | 4,476 (531 – 26,830) | 2,693 (0 – 22,968) | 49,422 (7,792 – 111,567) |
| Maximum, \$                                          | 120,927                 | 100,635                 | 114,153             | 107,553              | 44,362             | 506,108                  |
| Authors with payments (N=46), n (%)                  |                         |                         |                     |                      |                    |                          |
| Any payments                                         | 40 (87.0)               | 42 (91.3)               | 36 (78.3)           | 38 (82.6)            | 31 (73.9)          | 43 (93.5)                |
| >\$10,000                                            | 24 (52.2)               | 23 (50.0)               | 20 (43.5)           | 22 (47.8)            | 11 (41.3)          | 33 (71.7)                |
| >\$50,000                                            | 6 (13.0)                | 5 (10.9)                | 4 (8.7)             | 2 (4.4)              | 1 (6.5)            | 23 (50.0)                |
| >\$100,000                                           | 1 (2.2)                 | 1 (2.2)                 | 1 (2.2)             | 1 (2.2)              | 0 (0)              | 15 (32.6)                |
| >\$250,000                                           | 0 (0)                   | 0 (0)                   | 0 (0)               | 0 (0)                | 0 (0)              | 3 (6.5)                  |

Japanese yen (¥) were converted to US dollars (\$) using the 2020 average monthly exchange rate of ¥106 per \$1.

501 Table 3. Payment amounts by top 10 companies.  
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| Variables                                           | Payment amounts (%), \$ |                |                |                |              |                 |
|-----------------------------------------------------|-------------------------|----------------|----------------|----------------|--------------|-----------------|
|                                                     | 2016                    | 2017           | 2018           | 2019           | 2020         | Overall         |
| Total amounts of payments                           | 959,503 (100)           | 873,288 (100)  | 769,649 (100)  | 743,826 (100)  | 4,170 (100)  | 4,041,648 (100) |
| Top 10 companies making the largest payment amounts |                         |                |                |                |              |                 |
| Sumitomo Pharma                                     | 180,436 (18.8)          | 105,531 (12.1) | 127,847 (16.6) | 106,975 (14.4) | 4,243 (25.0) | 695,031 (17.2)  |
| Eisai                                               | 45,779 (4.8)            | 78,418 (9.0)   | 52,244 (6.8)   | 80,026 (10.8)  | 1,856 (21.8) | 408,323 (10.1)  |
| MSD                                                 | 122,880 (12.8)          | 83,528 (9.6)   | 79,420 (10.3)  | 57,679 (7.8)   | 1,020 (2.0)  | 357,526 (8.8)   |
| Otsuka Pharmaceutical                               | 64,794 (6.8)            | 73,028 (8.4)   | 64,161 (8.3)   | 86,679 (11.7)  | 1,976 (9.5)  | 354,638 (8.8)   |
| Takeda Pharmaceutical                               | 69,017 (7.2)            | 78,990 (9.0)   | 45,019 (5.8)   | 71,206 (9.6)   | 1,338 (10.5) | 337,370 (8.3)   |
| Pfizer Japan                                        | 78,269 (8.2)            | 106,973 (12.2) | 65,996 (8.6)   | 46,086 (6.2)   | 1,247 (2.0)  | 311,571 (7.7)   |
| Mitsubishi Tanabe Pharma                            | 58,501 (6.1)            | 47,295 (5.4)   | 61,056 (7.9)   | 59,114 (7.9)   | 2,789 (3.7)  | 251,755 (6.2)   |
| Eli Lilly Japan                                     | 56,337 (5.9)            | 60,899 (7.0)   | 59,231 (7.7)   | 36,314 (4.9)   | 3,130 (5.5)  | 250,910 (6.2)   |
| Meiji Seika Pharma                                  | 75,608 (7.9)            | 53,110 (6.1)   | 57,841 (7.5)   | 27,228 (3.7)   | 2,235 (3.5)  | 238,023 (5.9)   |
| Mochida Pharmaceutical                              | 35,768 (3.7)            | 29,405 (3.4)   | 31,597 (4.1)   | 41,378 (5.6)   | 1,209 (2.5)  | 155,356 (3.8)   |

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Table 4. Financial conflicts of interest self-declared by the guideline authors

| Disclosure category          | Number of authors reporting conflicts of interest<br>(%), n |                                  |
|------------------------------|-------------------------------------------------------------|----------------------------------|
|                              | Bipolar disorder (N=4)                                      | Major depressive disorder (N=14) |
| Speaking compensation        | 4 (100)                                                     | 11 (78.6)                        |
| Scholarship donation         | 3 (75.0)                                                    | 6 (42.9)                         |
| Consulting payments          | 0 (0)                                                       | 4 (28.6)                         |
| Collaborative research funds | 1 (25.0)                                                    | 2 (14.3)                         |
| Advisory board               | 2 (50.0)                                                    | 1 (7.1)                          |
| Contracted research funds    | 1 (25.0)                                                    | 0 (0)                            |

Legends: Proportion of authors reporting conflicts of interest were number of authors reporting conflicts of interest to the total number of writing authors.

BMJ Open-2024-086396 on 21 June 2024. Downloaded from <http://bmjopen.bmj.com/> on June 12, 2025 at Agence Bibliographique de l'Enseignement Supérieur (ABES) - AI training, and similar technologies.

STROBE Statement—checklist of items that should be included in reports of observational studies

|                           | Item No. | Recommendation                                                                                                                                                                       | Page No. | Relevant text from manuscript |
|---------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------------|
| Title and abstract        | 1        | (a) Indicate the study’s design with a commonly used term in the title or the abstract                                                                                               |          |                               |
|                           |          | (b) Provide in the abstract an informative and balanced summary of what was done and what was found                                                                                  |          |                               |
| Introduction              |          |                                                                                                                                                                                      |          |                               |
| Background/rationale      | 2        | Explain the scientific background and rationale for the investigation being reported                                                                                                 |          |                               |
| Objectives                | 3        | State specific objectives, including any prespecified hypotheses                                                                                                                     |          |                               |
| Methods                   |          |                                                                                                                                                                                      |          |                               |
| Study design              | 4        | Present key elements of study design early in the paper                                                                                                                              |          |                               |
| Setting                   | 5        | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                                                      |          |                               |
| Participants              | 6        | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up                                              |          |                               |
|                           |          | Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls   |          |                               |
|                           |          | Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants                                                                        |          |                               |
|                           |          | (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed                                                                                     |          |                               |
|                           |          | Case-control study—For matched studies, give matching criteria and the number of controls per case                                                                                   |          |                               |
|                           |          |                                                                                                                                                                                      |          |                               |
| Variables                 | 7        | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable                                             |          |                               |
| Data sources/ measurement | 8*       | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4        |                               |
| Bias                      | 9        | Describe any efforts to address potential sources of bias                                                                                                                            | n/a      |                               |
| Study size                | 10       | Explain how the study size was arrived at                                                                                                                                            | 3        |                               |

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|                        |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
|------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Quantitative variables | 11  | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why                                                                                                                                                                                                                                                                                                                                                                                                                                      |            |
| Statistical methods    | 12  | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed<br><i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed<br><i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses |            |
| <b>Results</b>         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
| Participants           | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram                                                                                                                                                                                                                                                                   |            |
| Descriptive data       | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)                                                                                                                                                                                                                                               |            |
| Outcome data           | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time<br><i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure<br><i>Cross-sectional study</i> —Report numbers of outcome events or summary measures                                                                                                                                                                                                                                                                                 |            |
| Main results           | 16  | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period                                                                                                                                                     | 4-5<br>n/a |

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|                          |    |                                                                                                                                                                            |
|--------------------------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other analyses           | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses                                                                             |
| <b>Discussion</b>        |    |                                                                                                                                                                            |
| Key results              | 18 | Summarise key results with reference to study objectives                                                                                                                   |
| Limitations              | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias                 |
| Interpretation           | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability         | 21 | Discuss the generalisability (external validity) of the study results                                                                                                      |
| <b>Other information</b> |    |                                                                                                                                                                            |
| Funding                  | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based              |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Cross-sectional analysis of pharmaceutical industry payments to authors of clinical practice guidelines for bipolar disorder and major depressive disorder in Japan

|                                 |                                                                                                                                                                                                                                                     |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Journal:                        | <i>BMJ Open</i>                                                                                                                                                                                                                                     |
| Manuscript ID                   | bmjopen-2024-086396.R1                                                                                                                                                                                                                              |
| Article Type:                   | Original research                                                                                                                                                                                                                                   |
| Date Submitted by the Author:   | 09-May-2024                                                                                                                                                                                                                                         |
| Complete List of Authors:       | Murayama, Anju; Tohoku University School of Medicine; Icahn School of Medicine at Mount Sinai, Department of Population Health Science and Policy<br>Kugo, Hinari; Tohoku University School of Medicine<br>Senoo, Yuki; Higashi Totsuka Kinen Byoin |
| <b>Primary Subject Heading</b>: | Ethics                                                                                                                                                                                                                                              |
| Secondary Subject Heading:      | Evidence based practice, Ethics, Health policy, Mental health                                                                                                                                                                                       |
| Keywords:                       | MEDICAL ETHICS, ETHICS (see Medical Ethics), Depression & mood disorders < PSYCHIATRY, PSYCHIATRY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT                                                                             |
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**Title: Cross-sectional analysis of pharmaceutical industry payments to authors of clinical practice guidelines for bipolar disorder and major depressive disorder in Japan**

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**Keywords:**

Conflicts of interest, pharmaceutical companies, clinical practice guideline, health policy, evidence-based medicine, ethics, depression, bipolar disorder

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**Abstract**

**Objective**

Clinical practice guidelines (CPGs) are essential for standardizing patient care based on evidence-based medicine. However, the presence of financial conflicts of interest (COIs) among CPG authors can undermine their credibility. This study aimed to examine the extent and size of COIs among authors of psychiatry CPGs in Japan.

**Methods**

This cross-sectional analysis of disclosed payments from pharmaceutical companies assesses the prevalence and magnitude of personal payments for lecturing, consulting, and writing to CPGs for bipolar disorder and major depressive disorder in Japan between 2016 and 2020.

**Results**

This study found that 93.3% of authors received payments over a five-year period, with total payments exceeding \$4 million. The median payment per author was \$51,403 (interquartile range: \$9,982 – \$111,567), with a notable concentration of payments among a small number of authors, including the CPG chairperson. Despite these extensive financial relationships, only a fraction of authors disclosed their COIs in the CPGs. These large amounts of personal payments were made by pharmaceutical companies manufacturing new antidepressants and sleeping aids listed in the CPGs.

**Conclusions**

This study found that more than 93% of authors of Japanese major depressive disorder and bipolar disorder CPGs received considerable amounts of personal payments from the pharmaceutical industry. The findings highlight deviations from international COI management standards and suggest a need for more stringent COI policies for psychiatry CPGs in Japan.

**Strengths and limitations**

This study utilized a publicly accessible database containing all lecturing, consulting, and writing payments to physicians disclosed by more than 70 pharmaceutical companies in Japan.

This is the first analysis examining amounts, fraction, and extent of financial ties between psychiatry guideline authors and pharmaceutical industry in Japan. However, the study could not cover financial interactions between the psychiatry guideline authors and pharmaceutical companies for research, royalties and licensing fees, ownership interests, and other miscellaneous fees.



## Introduction

Clinical practice guidelines (CPGs) have been increasingly used as a tool to endorse evidence-based medicine for healthcare professionals in their clinical practice.<sup>1 2</sup> CPGs aim to summarize the best available evidence and often include recommendations for specific diagnosis and treatment of specific diseases. Nevertheless, the integrity and recommendations of CPGs are frequently compromised by conflicts of interest (COIs) between the guideline authors and the pharmaceutical industry, spanning various medical specialties. In the field of psychiatry, there is documentation of ghostwriting by pharmaceutical industry<sup>3</sup> and widespread financial COIs between CPG authors and pharmaceutical companies.<sup>4-7</sup> Furthermore, studies showed that financial COIs are associated with a propensity for CPGs to make recommendations favorable to the healthcare industry in general.<sup>4 8</sup> This underscores the necessity for rigorous management of financial COIs among CPG authors, particularly in psychiatry.<sup>6 9 10</sup> A recent study demonstrated that 60% of panel members of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), fifth edition, text revision published by the American Psychiatry Association in 2022 received payments from the pharmaceutical industry.<sup>11</sup> As the DSM-5 is widely used as a standard for psychiatric disorders' definitions and symptom criteria, influencing treatment selection and approval of new drugs worldwide,<sup>11</sup> the widespread financial COIs among the DSM-5 panel members are concerning. However, financial COIs among psychiatry experts are not unique to international criteria and CPGs: they may also be problematic among authors of regional or national CPGs, as these guidelines include specific treatment recommendations that can influence the clinical practice of clinicians in each country or region.

To enhance the transparency of financial relationships between healthcare professionals and pharmaceutical companies, members of the Japan Pharmaceutical Manufacturers Association have voluntarily disclosed their financial interactions with healthcare professionals and organizations.<sup>12</sup> Subsequent research using this disclosed information has revealed that the vast majority of CPG authors in Japan received personal payments during the CPG development across various medical specialties.<sup>12-22</sup> However, these financial relationships between pharmaceutical companies and Japanese CPG authors in psychiatry remain largely unexplored. Considering the patterns observed in previous studies, we hypothesized that financial COIs are widespread among psychiatry CPG authors in Japan.

## Methods

### *Study setting and participants*

This cross-sectional analysis evaluated the extent and prevalence of financial interactions between pharmaceutical companies and authors of CPGs for major depressive disorder and bipolar disorder in Japan. Mood disorders, including bipolar disorder and major depressive disorder, are the most prevalent mental disorders in Japan. According to surveys conducted by the Japanese Ministry of Health, Labor, and Welfare, the number of patients with mood disorders has steadily increased over the past two decades, from 0.4 million in 1999 to 1.7 million in 2020.<sup>23</sup> The Japanese Society of Mood Disorders is responsible for the development of the sole CPGs for these conditions, namely Treatment Guideline I: Bipolar Disorder<sup>24</sup> and Treatment

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Guideline II: Major Depressive Disorder.<sup>25</sup> At the time of this study, the most recent versions were published in June 2020 and July 2019, respectively.

*Data collection*

The Japan Pharmaceutical Manufacturers Association, representing over 70 major pharmaceutical companies, mandates the disclosure of payments for lectures, consultancy, and writing to healthcare professionals, listing the recipients' names on company websites since 2013.<sup>26-28</sup> Despite annual updates and removal of previous years' data by these companies, the Medical Governance Research Institute has independently collected and disclosed this payment data on its public online database from 2016 to 2020, detailing individual physician and company names.<sup>29</sup>

Information about payments to CPG authors was extracted as follows. First, a list of the names of all CPG authors was created and saved as a CSV file. We then searched for their names in the payments database and extracted speaking, consulting, and writing payments to physicians whose names matched the CPG authors' names from the database using Python programming code. After extracting the relevant payment information, a manual review was performed to identify and remove any payments made to physicians whose names were similar to those of the CPG authors but who were actually different individuals, as we previously noted.<sup>30-33</sup> Finally, we randomly selected five CPG authors (representing 11.1% of all authors) and manually searched the authors' names in the payments database to ensure that the payment data extracted using Python were accurate and complete.

As the pharmaceutical companies have not individually disclosed other categories of non-research payments such as travel and accommodation fees, food and beverage fees, royalties and licensing fees, and ownership interests, this study incorporated all personal payments for lectures, consultancy, and writing from pharmaceutical companies to the CPG authors from 2016 to 2020, following the approach of prior studies.<sup>30 34-36</sup>

*Data analysis*

The study calculated the proportion of CPG authors receiving personal payments and assessed per-author payment amounts, including median, interquartile range, mean, and standard deviation.

We performed a sensitivity analysis examining personal payments to the CPG authors from 2016 to 2019, to evaluate financial relationships between the CPG authors and pharmaceutical companies before the CPG publication.

Additionally, we also calculated the proportion of authors receiving payments, total payment amounts, and median payment amounts by the roles of CPG authors.

Payments were converted from Japanese yen to US dollars using the 2020 average monthly exchange rate of 106.8 yen per \$1. Data extraction and analyses were executed using 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 a retrospective analysis of publicly available data, this study was classified as non-

human subjects research and did not require institutional review board approval in accordance with the Japanese Ministry of Health, Labor, and Welfare's Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

#### *Patient and public involvement*

No patients were involved in the preparation of this manuscript or the research project.

### **Results**

The study included 33 authors for the bipolar disorder CPG and 42 for the major depressive disorder CPG. Of these authors, 30 individual physicians contributed to both CPGs. Consequently, a total of 45 unique CPG authors were analyzed in this study.

Of all 45 authors, 42 (93.3%) received personal payments for lectures, consulting, and writing from pharmaceutical companies between 2016 and 2020 (Table 1). The total amount of personal payments received by the 55 pharmaceutical companies over the course of the study period was \$4,041,648. The median payment per author was \$51,403 (IQR: \$9,982 – \$111,567), and the mean payment was \$89,814 (SD: \$111,760), indicating a skewed distribution where a few authors received disproportionately high payments. Notably, 15 authors (33.3%) received in excess of \$100,000 over the five-year period. The majority of payments, constituting 65.8% (\$2.7 million) of the total, were for lecturing fees, with consulting and writing compensations accounting for 25.8% (\$1.0 million) and 8.3% (\$337,255) in total, respectively. All two chairs of each CPG development committee received personal payments from pharmaceutical companies totaling \$506,108 (the highest total) for the chair of the bipolar disorder CPG development committee and \$97,288 for the chair of the major depressive disorder CPG development committee over the five-year period.

Annual analysis revealed a decline in total payments to CPG authors from \$959,289 in 2016 to \$697,170 in 2020 (Table 1). Correspondingly, the median annual payment per author decreased from \$11,992 (IQR: \$1,877 – \$24,498) in 2016 to \$2,702 (IQR: \$120 – \$22,968) in 2020. The proportion of authors receiving payments also fell from 91.1% in 2017 to 75.6% in 2020, yet a majority still received at least one personal payment annually. The sensitivity analysis of payments to the CPG authors from 2016 to 2019 showed that 42 (93.2%) authors received at least one payment from pharmaceutical companies. The total amounts of personal payments were \$3,344,478 for the four-year period. Median amounts of four-year payments were \$44,688 (IQR: \$9,325 – \$93,393) per author.

Payments from the top 5 and 10 pharmaceutical companies constituted 53.3% (\$2.2 million) and 83.1% (\$3.4 million) of the total payments from 2016 to 2020, respectively (Table 2). Sumitomo Pharma made the largest total amounts of personal payments amounting to \$695,031 (17.2%), followed by Eisai (10.1%, \$408,323), MSD (8.8%, \$357,526), Otsuka Pharmaceutical (8.8%, \$354,638), and Takeda Pharmaceutical (8.3%, \$337,370). Among these companies, MSD, Pfizer Japan, and Meiji Seika notably reduced their personal payments from 2016 to 2020, whereas Eisai increased its

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payments from \$45,779 in 2016 to \$151,856 in 2020.

The two CPGs included three categories of author roles: writing authors, who were primarily responsible for developing the CPGs and making recommendations; supporting authors, who may have contributed to the CPG development in a limited capacity, such as identifying relevant evidence, performing literature reviews, and making recommendations for specific situations; and guideline development committee authors, who did not directly contribute to the creation of CPGs and recommendations but critically reviewed the initial CPG drafts and revised the drafts and recommendations. The CPGs explicitly indicated that all of these authors were involved in the formulation of recommendations.

Of three categories of author roles, all writing authors for both CPGs received personal payments from pharmaceutical companies between 2016 and 2020 (Table 3), while lower proportion of supporting authors received payments than those for writing authors and guideline development committee authors in both CPGs. Median payment amounts were the highest for writing authors (\$135,867 (IQR: \$78,553 – \$187,806) for the bipolar disorder CPG and \$87,610 (IQR: \$16,945 – \$111,567) for the major depressive disorder CPG).

Disclosure of financial COIs in the CPGs was self-reported only by writing authors. There were no COI declaration statements for other types of authors. All authors (100%, 4 out of 4) of the bipolar disorder CPG and 85.7% (12 out of 14) of the major depressive disorder CPG authors declared financial COIs with pharmaceutical companies. Table 4 presents the types of financial COIs self-reported by the CPG authors within each respective guideline. Among the six categories extracted from the disclosure statements in the CPGs, compensation for lecturing was the most frequently declared (100% for the bipolar disorder CPG authors and 78.6% for the major depressive disorder CPG authors). This was followed by scholarship donations and participation in pharmaceutical company advisory boards. Although there were discrepancies in the number of writing authors receiving payments between industry-sponsored payment data and authors' self-declared COI statements by payment/declaration category (Table 4), the lack of a specified declaration period precluded the assessment of the accuracy of each CPG author's self-reported COI statements against the payment data reported by the pharmaceutical companies.

**Discussion**

This cross-sectional analysis of publicly disclosed payment data from pharmaceutical companies provides a detailed examination of the extent and fraction of financial COIs among authors of the Japanese Society of Mood Disorders' Treatment Guideline I: Bipolar Disorder<sup>24</sup> and Treatment Guideline II: Major Depressive Disorder.<sup>25</sup> These CPGs are considered by physicians the authoritative and trustworthy sources for the treatment of bipolar disorder and major depressive disorder in Japan.<sup>37</sup> To the best of our knowledge, this is the first in-depth study to analyze the financial relationships between psychiatry CPG authors and pharmaceutical companies in Japan using pharmaceutical industry-disclosed data. The findings reveal that a large majority (93.3%) of CPG authors received personal payments for lecturing, consulting, and writing, with a total sum of \$4.0 million between 2016 and 2020. The median payment



per author was \$51,403, with a minority, including the CPG chairperson, receiving substantial sums. Nearly all authors involved in writing the CPGs self-reported financial COIs with pharmaceutical companies. Notably, the bulk of personal payments to CPG authors came from companies that manufacture antidepressants and sleeping pills in Japan. However, other CPG authors did not publicly disclose their financial COIs with these companies. When compared to previous studies and international COI policies for CPG authors, these findings raise concerns for physicians, patients, policymakers, and other stakeholders within and beyond Japan.

The study highlights that over 93% of the authors of CPGs for bipolar disorder and major depressive disorder had financial relationships with pharmaceutical industry. Given the publication dates of the CPGs between 2019 and 2020, these financial relationships likely occurred during the development of the CPGs. This high percentage of authors receiving personal payments aligns with findings from other specialties within Japan,<sup>12-15 17-22 31 33 38-42</sup> where the proportion of CPG authors with personal payments ranged from 66.0% in obstetrics and gynecology<sup>42</sup> to 96.3% in otolaryngology.

In contrast, research from other developed countries, such as the United States, reports lower proportions of CPG authors with financial COIs. For instance, 67% of authors for the DSM-5 mood disorders section disclosed financial COIs with the healthcare industry.<sup>9</sup> Additionally, a study by Cosgrove et al. found that only 18% of major depressive disorder CPG authors across eight countries had financial COIs with pharmaceutical companies.<sup>4 10</sup> In Canada, half of the authors of the CPG for depressive disorder developed by the Canadian Network for Mood and Anxiety Treatments reported financial COIs with the healthcare industry.<sup>43</sup> Other specialties in the United States also showed lower percentages, with 53% of gastroenterology CPG authors<sup>44</sup> and 59.3% of urology CPG authors receiving personal and/or research payments.<sup>45</sup> Moreover, Mooghali et al. reported that 73.7% of physician CPG authors in the United States received personal and/or research payments from healthcare companies.<sup>46</sup> The higher proportion of CPG authors receiving payments in Japan can be attributed to the fact that most professional medical societies in Japan have implemented less transparent COI policies. This is in line with our previous studies reporting on the matter.<sup>18 20</sup>

Furthermore, this investigation revealed that a select group of CPG authors, including the chairperson, received substantial personal payments from pharmaceutical companies. Only authors involved in writing the CPGs were mandated to declare their financial COIs, while other contributors did not publicly disclose any financial COIs with these companies. These results indicate that authors of Japanese CPGs for bipolar disorder and major depressive disorder clearly violate international COI policies on CPG development in several respects. The U.S. National Academy of Medicine's 2011 report and the Guidelines International Network advocate for a majority of CPG authors to be free from financial COIs.<sup>1 2</sup> These policies also stipulate that the chairperson of CPG development should not hold any COIs.<sup>1 2</sup> The Guideline Panel Review Working Group's criteria for red flags, as published in the British Medical Journal in 2013, indicate that financial COIs held by a CPG chairperson and multiple authors are significant concerns for the trustworthiness of the CPGs.<sup>47</sup> The prevalence of COIs

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299 exceeding 93% in this study is not a marginal discrepancy but a significant deviation  
300 from these standards, casting doubt on the objectivity and reliability of the guidelines.

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302 Moreover, the study revealed that substantial payments were made by pharmaceutical  
303 companies marketing new antidepressants and sleep aids in Japan. For example,  
304 Sumitomo Pharma, the top payer, produces lurasidone (brand name: Latuda), which was  
305 approved for bipolar disorder and schizophrenia in 2020, and has been co-marketing  
306 venlafaxine hydrochloride (brand name: Effexor) with Pfizer Japan since 2018. MSD,  
307 another major payer, produces suvorexant (brand name: Belsomra), the world's first  
308 orexin receptor antagonist used for insomnia. Otsuka Pharmaceutical is known as one of  
309 the major manufacturers of atypical antipsychotics, such as aripiprazole (brand name:  
310 Abilify) and brexpiprazole (brand name: Rexulti), which are the most widely prescribed  
311 atypical antipsychotics in Japan.<sup>48</sup> Despite these financial ties between CPG authors and  
312 pharmaceutical companies manufacturing relevant drugs, the Japanese Society of Mood  
313 Disorders actively endorses adherence to these CPGs.<sup>49 50</sup> Given that the CPGs for  
314 bipolar disorder and major depressive disorder include pharmacotherapy  
315 recommendations that include medications from these companies, it is imperative that  
316 the close financial ties between CPG authors and the pharmaceutical industry be  
317 addressed. We strongly recommend the Japanese Society of Mood Disorders to enforce  
318 more transparent and stringent COI management strategies in the CPG development  
319 process for bipolar disorder and major depressive disorder to ensure the integrity and  
320 credibility of these guidelines.

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322 *Limitations*

323 This study is subject to several limitations. Primarily, the study focus on CPGs for  
324 bipolar disorder and major depressive disorder in Japan would limit the generalizability  
325 of our findings to other medical fields or countries. Additionally, the payment data were  
326 derived from a secondary source, the Medical Governance Research Institute's database,  
327 which contains payment information from member companies of the Japan  
328 Pharmaceutical Manufacturers Association for the period 2016-2020.<sup>27 51</sup> Absent legal  
329 mandates for precise payment disclosures in Japan, the potential for inaccuracies or  
330 underreporting in the database cannot be discounted. Furthermore, the voluntary nature  
331 of these disclosures means that financial interactions between CPG authors and non-  
332 disclosing pharmaceutical entities may remain undetected. Nevertheless, given that the  
333 member companies account for 80% of the market share for drugs and medical products  
334 in Japan,<sup>52</sup> the impact of financial relationships between the CPG authors and uncovered  
335 companies would be minimized.

336  
337 *Conclusions*

338 More than 93% of the authors of the Treatment Guidelines for Bipolar Disorder and  
339 Major Depressive Disorder developed by the Japanese Society of Mood Disorders  
340 received personal payments for the reimbursement of their lecturing, consulting, and  
341 writing activities from the pharmaceutical companies manufacturing related drugs. The  
342 total amounts of personal payments to the CPG authors were more than \$4.0 million  
343 over the five years. Nevertheless, the financial COIs were only declared by the limited  
344 group of CPG authors. Further transparent and rigorous COI management strategies  
345 must be warranted in the Japanese Society of Mood Disorders.



### Author contribution:

A.M. contributed to data collection, resource, software, formal analysis, visualization, supervision, and study administration. All authors (A.M., H.K., and Y.S.) contributed to study conceptualization, methodology, writing the original draft, and reviewing the draft.

### Conflicts of interest:

The authors declare that there were no conflicts of interest for this study.

### Funding sources:

The authors declare that there were no funding sources for this study.

### IRB Statement

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's Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

### Declaration of generative AI in scientific writing

During the preparation of this work, the authors used ChatGPT version 4.0 solely for the purpose of identifying and correcting grammatical and spelling errors, and we did not use it for the creation of any intellectual parts of the manuscript. After using this tool, the authors carefully reviewed and edited the content as needed and take full responsibility for the content of the publication.

### Data availability statement:

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 privacy protection, payment data of individual CPG authors will be available from the corresponding author upon reasonable request.

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Table 1. Summary of personal payments from pharmaceutical companies to psychiatry clinical practice guideline authors from 2016 to 2020

| Variables                                            | 2016                    | 2017                    | 2018                   | 2019                 | 2020               | Four-year total amounts from 2016 to 2019 | Five-year total amounts from 2016 to 2020 |
|------------------------------------------------------|-------------------------|-------------------------|------------------------|----------------------|--------------------|-------------------------------------------|-------------------------------------------|
| Total amount of payments, \$                         | 959,289                 | 872,245                 | 769,649                | 743,295              | 697,100            | 3,344,478                                 | 4,041,648                                 |
| Mean payments per author (standard deviation), \$    | 21,318 (27,281)         | 19,383 (24,380)         | 17,103 (24,797)        | 16,518 (21,363)      | 15,400 (22,338)    | 74,322 (93,767)                           | 89,814 (111,760)                          |
| Median payments per author (interquartile range), \$ | 11,992 (1,877 – 24,498) | 10,678 (2,309 – 25,058) | 5,452 (1,251 – 22,591) | 4,506 (834 – 26,830) | 2,701 (0 – 22,900) | 44,688 (9,325 – 93,393)                   | 51,403 (9,982 – 111,567)                  |
| Maximum payment amounts, \$                          | 120,927                 | 100,635                 | 114,153                | 107,553              | 94,333             | 411,745                                   | 506,108                                   |
| Authors receiving personal payments (N=45), n (%)    |                         |                         |                        |                      |                    |                                           |                                           |
| Any payments                                         | 39 (86.7)               | 41 (91.1)               | 36 (80.0)              | 37 (82.2)            | 34 (75.6)          | 42 (93.3)                                 | 42 (93.3)                                 |
| >\$10,000                                            | 24 (53.3)               | 23 (51.1)               | 20 (44.4)              | 22 (48.9)            | 19 (42.2)          | 32 (71.1)                                 | 33 (73.3)                                 |
| >\$50,000                                            | 6 (13.3)                | 5 (11.1)                | 4 (8.9)                | 2 (4.4)              | 3 (6.7)            | 21 (46.7)                                 | 23 (51.1)                                 |
| >\$100,000                                           | 1 (2.2)                 | 1 (2.2)                 | 1 (2.2)                | 1 (2.2)              | 0 (0)              | 10 (22.2)                                 | 15 (33.3)                                 |
| >\$250,000                                           | 0 (0)                   | 0 (0)                   | 0 (0)                  | 0 (0)                | 0 (0)              | 2 (4.4)                                   | 3 (6.7)                                   |

Japanese yen (¥) were converted to US dollars (\$) using the 2020 average monthly exchange rate of ¥106 per \$1.

Table 2. Payment amounts by top 10 companies.

| Variables                                           | Payment amounts (%), \$ |                |                |                |                |                 | Major products used for bipolar and major depressive disorders (generic name)                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------|-------------------------|----------------|----------------|----------------|----------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                     | 2016                    | 2017           | 2018           | 2019           | 2020           | 2021            |                                                                                                                                                                                                                                                                                                                                                          |
| Total amounts of payments                           | 959,289 (100)           | 872,245 (100)  | 769,649 (100)  | 743,295 (100)  | 697,170 (100)  | 4,000,000 (100) |                                                                                                                                                                                                                                                                                                                                                          |
| Top 10 companies making the largest payment amounts |                         |                |                |                |                |                 |                                                                                                                                                                                                                                                                                                                                                          |
| Sumitomo Pharma                                     | 180,436 (18.8)          | 105,531 (12.1) | 127,847 (16.6) | 106,975 (14.4) | 174,243 (25.0) | 697,170 (17.4)  | Effexor (venlafaxine, co-promotion with Pfizer Japan)<br>Erispan (fludiazepam)<br>Excegran (zonisamide)<br>Halomonth (haloperidol decanoate)<br>Mystan (clobazam)<br>Noritren (nortriptyline)<br>Landosen (clonazepam)<br>Latuda (lurasidone)<br>Lonasen Tapes (blonanserin)<br>Lullan (perospirone)<br>Sediell (tandospirone)<br>Serenace (haloperidol) |
| Eisai                                               | 45,779 (4.8)            | 78,418 (9.0)   | 52,244 (6.8)   | 80,026 (10.8)  | 151,856 (21.8) | 408,353 (10.2)  | Dayvigo (lemborexant)<br>Spriprotan spiperone                                                                                                                                                                                                                                                                                                            |
| MSD                                                 | 122,880 (12.8)          | 83,528 (9.6)   | 79,420 (10.3)  | 57,679 (7.8)   | 14,020 (2.0)   | 357,526 (8.8)   | Belsomra (suvorexant)<br>Remeron (mirtazapine)<br>Reslin (trazodone)                                                                                                                                                                                                                                                                                     |



|                             |              |                   |              |               |               |               |                                                                                                                                                                                                                                                           |
|-----------------------------|--------------|-------------------|--------------|---------------|---------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |              |                   |              |               |               |               | Tetramide (mianserin)                                                                                                                                                                                                                                     |
| Otsuka<br>Pharmaceutical    | 64,794 (6.8) | 73,028 (8.4)      | 64,161 (8.3) | 86,679 (11.7) | 65,976 (9.5)  | 354,538 (8.8) | Abilify (aripiprazole)<br>Rexulti (brexpiprazole)                                                                                                                                                                                                         |
| Takeda<br>Pharmaceutical    | 69,017 (7.2) | 78,990 (9.1)      | 45,019 (5.8) | 71,206 (9.6)  | 73,138 (10.5) | 337,538 (8.3) | Depas (etizolam)<br>Eurodin (estazolam)<br>Trintellix (vortioxetine)                                                                                                                                                                                      |
| Pfizer Japan                | 78,269 (8.2) | 106,973<br>(12.3) | 65,996 (8.6) | 46,086 (6.2)  | 14,247 (2.0)  | 311,571 (7.7) | Amoxan (amoxapine)<br>Desyrel (trazodone)<br>Effexor (venlafaxin)<br>Halcion (triazolam)<br>Jzoloft (sertraline)<br>Wypax (lorazepam)<br>Fluvoxamine (generic<br>fluvoxamine)<br>Milnacipran (generic<br>milnacipran)<br>Mirtzapin (generic<br>mirtzapin) |
| Mitsubishi<br>Tanabe Pharma | 58,501 (6.1) | 47,295 (5.4)      | 61,056 (7.9) | 59,114 (8.0)  | 25,789 (3.7)  | 251,555 (6.2) | Clofekton<br>(clocapramine<br>hydrochloride)<br>Contomin<br>(chlorpromazine)<br>Levotomin<br>(levomepromazine)<br>Rize (clotiazepam)                                                                                                                      |
| Eli Lilly Japan             | 56,337 (5.9) | 60,899 (7.0)      | 59,231 (7.7) | 36,314 (4.9)  | 38,130 (5.5)  | 250,910 (6.2) | Strattera (atomoxetine)<br>Zyprexa (olanzapine)<br>Zyprexa Zydis<br>(olanzapine)                                                                                                                                                                          |
| Meiji Seika<br>Pharma       | 75,608 (7.9) | 53,110 (6.1)      | 57,841 (7.5) | 27,228 (3.7)  | 24,235 (3.5)  | 238,023 (5.9) | Depromel<br>(fluvoxamine)                                                                                                                                                                                                                                 |

|                           |              |              |              |              |              |               |                                                                                       |
|---------------------------|--------------|--------------|--------------|--------------|--------------|---------------|---------------------------------------------------------------------------------------|
|                           |              |              |              |              |              |               | Reflex (mirtazapine)<br>Sycrest (asenapine)<br>Aripiprazole (generic<br>aripiprazole) |
| Mochida<br>Pharmaceutical | 35,768 (3.7) | 29,405 (3.4) | 31,597 (4.1) | 41,378 (5.6) | 17,209 (2.5) | 155,000 (3.8) | Lexapro (escitalopram)<br>Tecipul (setiptiline)<br>Zolpidem (generic<br>zolpidem)     |

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Table 3. Payments by author categories in the bipolar disorder and major depressive disorder clinical practice guidelines

| Variables                                                   | Guideline disease category |                           |
|-------------------------------------------------------------|----------------------------|---------------------------|
|                                                             | Bipolar disorder           | Major depressive disorder |
| Number of all authors, N                                    | 33                         | 42                        |
| Role of guideline authors, n (%)                            |                            |                           |
| Writing authors <sup>a</sup>                                | 4 (12.1)                   | 14 (33.3)                 |
| Supporting authors <sup>b</sup>                             | 5 (15.2)                   | 12 (28.6)                 |
| Guideline development committee authors <sup>c</sup>        | 24 (72.7)                  | 16 (38.1)                 |
| Payments by author roles                                    |                            |                           |
| Total payment amounts, \$                                   |                            |                           |
| Writing authors <sup>a</sup>                                | 532,717                    | 1,659,595                 |
| Supporting authors <sup>b</sup>                             | 12,140                     | 930,986                   |
| Guideline development committee authors <sup>c</sup>        | 2,548,718                  | 1,448,508                 |
| Number of authors receiving payments by author roles, n (%) |                            |                           |
| Writing authors <sup>a</sup>                                | 4 (100)                    | 14 (100)                  |
| Supporting authors <sup>b</sup>                             | 4 (80.0)                   | 10 (83.3)                 |
| Guideline development committee authors <sup>c</sup>        | 22 (91.7)                  | 16 (100)                  |
| Median payment amounts per author, \$                       |                            |                           |
| Writing authors <sup>a</sup>                                | 135,867 (78,553 – 187,806) | 87,610 (16,945 – 111,567) |
| Supporting authors <sup>b</sup>                             | 1,788 (715 – 1,845)        | 60,120 (1,573 – 142,732)  |
| Guideline development committee authors <sup>c</sup>        | 34,569 (11,588 – 184,068)  | 34,569 (14,331 – 149,624) |

<sup>a</sup> Writing authors directly contributed to the creation of guidelines.

<sup>b</sup> Supporting authors could have contributed to identifying relevant evidence and performing literature reviews.

<sup>c</sup> Guideline development committee authors were not directly involved in the creation of the guidelines, but critically reviewed the contents and recommendations of the initial guideline draft and revised them if necessary.

Table 4. Financial conflicts of interest self-declared by the guideline authors

| Variables                                                                                 | Bipolar disorder (N=4) | Major depressive disorder (N=14) |
|-------------------------------------------------------------------------------------------|------------------------|----------------------------------|
| Number of authors self-reporting conflicts of interest by category                        |                        |                                  |
| Speaking compensation                                                                     | 4 (100)                | 11 (78.6)                        |
| Scholarship donation                                                                      | 3 (75.0)               | 6 (42.9)                         |
| Consulting payments                                                                       | 0 (0)                  | 4 (28.6)                         |
| Collaborative research funds                                                              | 1 (25.0)               | 2 (14.3)                         |
| Advisory board                                                                            | 2 (50.0)               | 1 (7.1)                          |
| Contracted research funds                                                                 | 1 (25.0)               | 0 (0)                            |
| Any category                                                                              | 4 (100)                | 12 (85.7)                        |
| Industry-reported payments to authors                                                     |                        |                                  |
| Number of writing authors receiving payments from 2016 to 2020 by payment category, n (%) |                        |                                  |
| Lecturing payments                                                                        | 4 (100)                | 14 (100)                         |
| Consulting payments                                                                       | 4 (100)                | 12 (85.7)                        |
| Writing payments                                                                          | 4 (100)                | 9 (64.3)                         |
| Any payment category                                                                      | 4 (100)                | 14 (100)                         |
| Total payment amounts to writing authors from 2016 to 2020, \$                            |                        |                                  |
| Lecturing payments                                                                        | 399,929                | 1,073,071                        |
| Consulting payments                                                                       | 101,805                | 430,660                          |
| Writing payments                                                                          | 30,983                 | 155,864                          |

Legends: Proportion of authors reporting conflicts of interest were number of authors reporting conflicts of interest to the total number of writing authors.

## STROBE Statement—checklist of items that should be included in reports of observational studies

|                           | Item No. | Recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Page No. | Relevant text from manuscript |
|---------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------------|
| <b>Title and abstract</b> | 1        | (a) Indicate the study's design with a commonly used term in the title or the abstract<br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |          |                               |
| <b>Introduction</b>       |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |                               |
| Background/rationale      | 2        | Explain the scientific background and rationale for the investigation being reported                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |          |                               |
| Objectives                | 3        | State specific objectives, including any prespecified hypotheses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |
| <b>Methods</b>            |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |                               |
| Study design              | 4        | Present key elements of study design early in the paper                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |          |                               |
| Setting                   | 5        | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |                               |
| Participants              | 6        | (a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br><i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br><i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants<br>(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed<br><i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case |          |                               |
| Variables                 | 7        | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |          |                               |
| Data sources/measurement  | 8*       | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 4        |                               |
| Bias                      | 9        | Describe any efforts to address potential sources of bias                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | n/a      |                               |
| Study size                | 10       | Explain how the study size was arrived at                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 3        |                               |

Continued on next page



|                        |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
|------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Quantitative variables | 11  | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why                                                                                                                                                                                                                                                                                                                                                                                                                                      |            |
| Statistical methods    | 12  | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed<br><i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed<br><i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses |            |
| <b>Results</b>         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
| Participants           | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram                                                                                                                                                                                                                                                                   |            |
| Descriptive data       | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)                                                                                                                                                                                                                                               |            |
| Outcome data           | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time<br><i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure<br><i>Cross-sectional study</i> —Report numbers of outcome events or summary measures                                                                                                                                                                                                                                                                                 |            |
| Main results           | 16  | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period                                                                                                                                                     | 5-6<br>n/a |

Continued on next page

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|                          |    |                                                                                                                                                                            |
|--------------------------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other analyses           | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses                                                                             |
| <b>Discussion</b>        |    |                                                                                                                                                                            |
| Key results              | 18 | Summarise key results with reference to study objectives                                                                                                                   |
| Limitations              | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias                 |
| Interpretation           | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability         | 21 | Discuss the generalisability (external validity) of the study results                                                                                                      |
| <b>Other information</b> |    |                                                                                                                                                                            |
| Funding                  | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based              |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Cross-sectional analysis of pharmaceutical industry payments to authors of clinical practice guidelines for bipolar disorder and major depressive disorder in Japan

|                                 |                                                                                                                                                                                                                                                     |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Journal:                        | <i>BMJ Open</i>                                                                                                                                                                                                                                     |
| Manuscript ID                   | bmjopen-2024-086396.R2                                                                                                                                                                                                                              |
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| Complete List of Authors:       | Murayama, Anju; Tohoku University School of Medicine; Icahn School of Medicine at Mount Sinai, Department of Population Health Science and Policy<br>Kugo, Hinari; Tohoku University School of Medicine<br>Senoo, Yuki; Higashi Totsuka Kinen Byoin |
| <b>Primary Subject Heading</b>: | Ethics                                                                                                                                                                                                                                              |
| Secondary Subject Heading:      | Evidence based practice, Ethics, Health policy, Mental health                                                                                                                                                                                       |
| Keywords:                       | MEDICAL ETHICS, ETHICS (see Medical Ethics), Depression & mood disorders < PSYCHIATRY, PSYCHIATRY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT                                                                             |
|                                 |                                                                                                                                                                                                                                                     |

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**Title: Cross-sectional analysis of pharmaceutical industry payments to authors of clinical practice guidelines for bipolar disorder and major depressive disorder in Japan**

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**Keywords:**

Conflicts of interest, pharmaceutical companies, clinical practice guideline, health policy, evidence-based medicine, ethics, depression, bipolar disorder

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**Abstract**

**Objective**

Clinical practice guidelines (CPGs) are essential for standardizing patient care based on evidence-based medicine. However, the presence of financial conflicts of interest (COIs) among CPG authors can undermine their credibility. This study aimed to examine the extent and size of COIs among authors of psychiatry CPGs in Japan.

**Methods**

This cross-sectional analysis of disclosed payments from pharmaceutical companies assesses the prevalence and magnitude of personal payments for lecturing, consulting, and writing to CPGs for bipolar disorder and major depressive disorder in Japan between 2016 and 2020.

**Results**

This study found that 93.3% of authors received payments over a five-year period, with total payments exceeding \$4 million. The median payment per author was \$51,403 (interquartile range: \$9,982 – \$111,567), with a notable concentration of payments among a small number of authors, including the CPG chairperson. Despite these extensive financial relationships, only a fraction of authors disclosed their COIs in the CPGs. These large amounts of personal payments were made by pharmaceutical companies manufacturing new antidepressants and sleeping aids listed in the CPGs.

**Conclusions**

This study found that more than 93% of authors of Japanese major depressive disorder and bipolar disorder CPGs received considerable amounts of personal payments from the pharmaceutical industry. The findings highlight deviations from international COI management standards and suggest a need for more stringent COI policies for psychiatry CPGs in Japan.

**Strengths and limitations**

- This study utilized a publicly accessible database containing all payments to physicians for lecturing, consulting, and writing disclosed by over 70 pharmaceutical companies in Japan.
- All authors of the clinical guidelines for major depressive disorder and bipolar disorder published by the Japanese Society of Mood Disorders were included in this study.
- The study was unable to encompass other types of payments to the guideline authors such as research, royalties, licensing fees, ownership interests, and other miscellaneous fees.
- There might be payments to the guideline authors that are under-disclosed and/or undisclosed by the pharmaceutical companies.

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## Introduction

Clinical practice guidelines (CPGs) have been increasingly used as a tool to endorse evidence-based medicine for healthcare professionals in their clinical practice.<sup>1 2</sup> CPGs aim to summarize the best available evidence and often include recommendations for specific diagnosis and treatment of specific diseases. Nevertheless, the integrity and recommendations of CPGs are frequently compromised by conflicts of interest (COIs) between the guideline authors and the pharmaceutical industry, spanning various medical specialties. In the field of psychiatry, there is documentation of ghostwriting by pharmaceutical industry<sup>3</sup> and widespread financial COIs between CPG authors and pharmaceutical companies.<sup>4-7</sup> Furthermore, studies showed that financial COIs are associated with a propensity for CPGs to make recommendations favorable to the healthcare industry in general.<sup>4 8</sup> This underscores the necessity for rigorous management of financial COIs among CPG authors, particularly in psychiatry.<sup>6 9 10</sup> A recent study demonstrated that 60% of panel members of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), fifth edition, text revision published by the American Psychiatry Association in 2022 received payments from the pharmaceutical industry.<sup>11</sup> As the DSM-5 is widely used as a standard for psychiatric disorders' definitions and symptom criteria, influencing treatment selection and approval of new drugs worldwide,<sup>11</sup> the widespread financial COIs among the DSM-5 panel members are concerning. However, financial COIs among psychiatry experts are not unique to international criteria and CPGs: they may also be problematic among authors of regional or national CPGs, as these guidelines include specific treatment recommendations that can influence the clinical practice of clinicians in each country or region.

To enhance the transparency of financial relationships between healthcare professionals and pharmaceutical companies, members of the Japan Pharmaceutical Manufacturers Association have voluntarily disclosed their financial interactions with healthcare professionals and organizations.<sup>12</sup> Subsequent research using this disclosed information has revealed that the vast majority of CPG authors in Japan received personal payments during the CPG development across various medical specialties.<sup>12-22</sup> However, these financial relationships between pharmaceutical companies and Japanese CPG authors in psychiatry remain largely unexplored. Considering the patterns observed in previous studies, we hypothesized that financial COIs are widespread among psychiatry CPG authors in Japan.

## Methods

### *Study setting and participants*

This cross-sectional analysis evaluated the extent and prevalence of financial interactions between pharmaceutical companies and authors of CPGs for major depressive disorder and bipolar disorder in Japan. Mood disorders, including bipolar disorder and major depressive disorder, are the most prevalent mental disorders in Japan. According to surveys conducted by the Japanese Ministry of Health, Labor, and Welfare, the number of patients with mood disorders has steadily increased over the past two decades, from 0.4 million in 1999 to 1.7 million in 2020.<sup>23</sup> The Japanese Society of Mood Disorders is responsible for the development of the sole CPGs for these conditions, namely Treatment Guideline I: Bipolar Disorder<sup>24</sup> and Treatment Guideline II: Major Depressive Disorder.<sup>25</sup> At the time of this study, the most recent versions were published in June 2020 and July 2019, respectively.

### *Data collection*

The Japan Pharmaceutical Manufacturers Association, representing over 70 major pharmaceutical companies, mandates the disclosure of payments for lectures, consultancy, and writing to healthcare professionals, listing the recipients' names on company websites since 2013.<sup>26-28</sup> Despite annual

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updates and removal of previous years' data by these companies, the Medical Governance Research Institute has independently collected and disclosed this payment data on its public online database from 2016 to 2020, detailing individual physician and company names.<sup>29</sup>

Information about payments to CPG authors was extracted as follows. First, a list of the names of all CPG authors was created and saved as a CSV file. We then searched for their names in the payments database and extracted speaking, consulting, and writing payments to physicians whose names matched the CPG authors' names from the database using Python programming code. After extracting the relevant payment information, a manual review was performed to identify and remove any payments made to physicians whose names were similar to those of the CPG authors but who were actually different individuals, as we previously noted.<sup>30-33</sup> Finally, we randomly selected five CPG authors (representing 11.1% of all authors) and manually searched the authors' names in the payments database to ensure that the payment data extracted using Python were accurate and complete.

As the pharmaceutical companies have not individually disclosed other categories of non-research payments such as travel and accommodation fees, food and beverage fees, royalties and licensing fees, and ownership interests, this study incorporated all personal payments for lectures, consultancy, and writing from pharmaceutical companies to the CPG authors from 2016 to 2020, following the approach of prior studies.<sup>30 34-36</sup>

*Data analysis*

The study calculated the proportion of CPG authors receiving personal payments and assessed per-author payment amounts, including median, interquartile range, mean, and standard deviation. We performed a sensitivity analysis examining personal payments to the CPG authors from 2016 to 2019, to evaluate financial relationships between the CPG authors and pharmaceutical companies before the CPG publication. Additionally, we also calculated the proportion of authors receiving payments, total payment amounts, and median payment amounts by the roles of CPG authors. Payments were converted from Japanese yen to US dollars using the 2020 average monthly exchange rate of 106.8 yen per \$1. Data extraction and analyses were executed using 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 a retrospective analysis of publicly available data, this study was classified as non-human subjects research and did not require institutional review board approval in accordance with the Japanese Ministry of Health, Labor, and Welfare's Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

*Patient and public involvement*

No patients were involved in the preparation of this manuscript or the research project.

**Results**

The study included 33 authors for the bipolar disorder CPG and 42 for the major depressive disorder CPG. Of these authors, 30 individual physicians contributed to both CPGs. Consequently, a total of 45 unique CPG authors were analyzed in this study.

Of all 45 authors, 42 (93.3%) received personal payments for lectures, consulting, and writing from pharmaceutical companies between 2016 and 2020 (Table 1). The total amount of personal payments received by the 55 pharmaceutical companies over the course of the study period was \$4,041,648. The median payment per author was \$51,403 (IQR: \$9,982 – \$111,567), and the mean payment was \$89,814 (SD: \$111,760), indicating a skewed distribution where a few authors received disproportionately high payments. Notably, 15 authors (33.3%) received in excess of \$100,000 over the five-year period. The majority of payments, constituting 65.8% (\$2.7 million) of the total, were for lecturing fees, with consulting and writing compensations accounting for 25.8% (\$1.0 million) and 8.3% (\$337,255) in total, respectively. All two chairs of each CPG development committee received personal payments from pharmaceutical companies totaling \$506,108 (the highest total) for the chair of the bipolar disorder CPG development committee and \$97,288 for the chair of the major depressive disorder CPG development committee over the five-year period.

Annual analysis revealed a decline in total payments to CPG authors from \$959,289 in 2016 to \$697,170 in 2020 (Table 1). Correspondingly, the median annual payment per author decreased from \$11,992 (IQR: \$1,877 – \$24,498) in 2016 to \$2,702 (IQR: \$120 – \$22,968) in 2020. The proportion of authors receiving payments also fell from 91.1% in 2017 to 75.6% in 2020, yet a majority still received at least one personal payment annually. The sensitivity analysis of payments to the CPG authors from 2016 to 2019 showed that 42 (93.2%) authors received at least one payment from pharmaceutical companies. The total amounts of personal payments were \$3,344,478 for the four-year period. Median amounts of four-year payments were \$44,688 (IQR: \$9,325 – \$93,393) per author.

Payments from the top 5 and 10 pharmaceutical companies constituted 53.3% (\$2.2 million) and 83.1% (\$3.4 million) of the total payments from 2016 to 2020, respectively (Table 2). Sumitomo Pharma made the largest total amounts of personal payments amounting to \$695,031 (17.2%), followed by Eisai (10.1%, \$408,323), MSD (8.8%, \$357,526), Otsuka Pharmaceutical (8.8%, \$354,638), and Takeda Pharmaceutical (8.3%, \$337,370). Among these companies, MSD, Pfizer Japan, and Meiji Seika notably reduced their personal payments from 2016 to 2020, whereas Eisai increased its payments from \$45,779 in 2016 to \$151,856 in 2020.

The two CPGs included three categories of author roles: writing authors, who were primarily responsible for developing the CPGs and making recommendations; supporting authors, who may have contributed to the CPG development in a limited capacity, such as identifying relevant evidence, performing literature reviews, and making recommendations for specific situations; and guideline development committee authors, who did not directly contribute to the creation of CPGs and recommendations but critically reviewed the initial CPG drafts and revised the drafts and recommendations. The CPGs explicitly indicated that all of these authors were involved in the formulation of recommendations.

Of three categories of author roles, all writing authors for both CPGs received personal payments from pharmaceutical companies between 2016 and 2020 (Table 3), while lower proportion of supporting authors received payments than those for writing authors and guideline development committee authors in both CPGs. Median payment amounts were the highest for writing authors (\$135,867 (IQR: \$78,553 – \$187,806) for the bipolar disorder CPG and \$87,610 (IQR: \$16,945 – \$111,567) for the major depressive disorder CPG).

Disclosure of financial COIs in the CPGs was self-reported only by writing authors. There were no COI declaration statements for other types of authors. All authors (100%, 4 out of 4) of the bipolar disorder CPG and 85.7% (12 out of 14) of the major depressive disorder CPG authors declared

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3 207 financial COIs with pharmaceutical companies. Table 4 presents the types of financial COIs self-  
4 208 reported by the CPG authors within each respective guideline. Among the six categories extracted  
5 209 from the disclosure statements in the CPGs, compensation for lecturing was the most frequently  
6 210 declared (100% for the bipolar disorder CPG authors and 78.6% for the major depressive disorder  
7 211 CPG authors). This was followed by scholarship donations and participation in pharmaceutical  
8 212 company advisory boards. Although there were discrepancies in the number of writing authors  
9 213 receiving payments between industry-sponsored payment data and authors' self-declared COI  
10 214 statements by payment/declaration category (Table 4), the lack of a specified declaration period  
11 215 precluded the assessment of the accuracy of each CPG author's self-reported COI statements against  
12 216 the payment data reported by the pharmaceutical companies.  
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16 218 **Discussion**

17 219 This cross-sectional analysis of publicly disclosed payment data from pharmaceutical companies  
18 220 provides a detailed examination of the extent and fraction of financial COIs among authors of the  
19 221 Japanese Society of Mood Disorders' Treatment Guideline I: Bipolar Disorder<sup>24</sup> and Treatment  
20 222 Guideline II: Major Depressive Disorder.<sup>25</sup> These CPGs are considered by physicians the  
21 223 authoritative and trustworthy sources for the treatment of bipolar disorder and major depressive  
22 224 disorder in Japan.<sup>37</sup> To the best of our knowledge, this is the first in-depth study to analyze the  
23 225 financial relationships between psychiatry CPG authors and pharmaceutical companies in Japan  
24 226 using pharmaceutical industry-disclosed data. The findings reveal that a large majority (93.3%) of  
25 227 CPG authors received personal payments for lecturing, consulting, and writing, with a total sum of  
26 228 \$4.0 million between 2016 and 2020. The median payment per author was \$51,403, with a minority,  
27 229 including the CPG chairperson, receiving substantial sums. Nearly all authors involved in writing the  
28 230 CPGs self-reported financial COIs with pharmaceutical companies. Notably, the bulk of personal  
29 231 payments to CPG authors came from companies that manufacture antidepressants and sleeping pills  
30 232 in Japan. However, other CPG authors did not publicly disclose their financial COIs with these  
31 233 companies. When compared to previous studies and international COI policies for CPG authors,  
32 234 these findings raise concerns for physicians, patients, policymakers, and other stakeholders within  
33 235 and beyond Japan.  
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38 237 The study highlights that over 93% of the authors of CPGs for bipolar disorder and major depressive  
39 238 disorder had financial relationships with pharmaceutical industry. Given the publication dates of the  
40 239 CPGs between 2019 and 2020, these financial relationships likely occurred during the development  
41 240 of the CPGs. This high percentage of authors receiving personal payments aligns with findings from  
42 241 other specialties within Japan,<sup>12-15 17-22 31 33 38-42</sup> where the proportion of CPG authors with personal  
43 242 payments ranged from 66.0% in obstetrics and gynecology<sup>42</sup> to 96.3% in otolaryngology.  
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46 244 In contrast, research from other developed countries, such as the United States, reports lower  
47 245 proportions of CPG authors with financial COIs. For instance, 67% of authors for the DSM-5 mood  
48 246 disorders section disclosed financial COIs with the healthcare industry.<sup>9</sup> Additionally, a study by  
49 247 Cosgrove et al. found that only 18% of major depressive disorder CPG authors across eight countries  
50 248 had financial COIs with pharmaceutical companies.<sup>4 10</sup> In Canada, half of the authors of the CPG for  
51 249 depressive disorder developed by the Canadian Network for Mood and Anxiety Treatments reported  
52 250 financial COIs with the healthcare industry.<sup>43</sup> Other specialties in the United States also showed  
53 251 lower percentages, with 53% of gastroenterology CPG authors<sup>44</sup> and 59.3% of urology CPG authors  
54 252 receiving personal and/or research payments.<sup>45</sup> Moreover, Mooghali et al. reported that 73.7% of  
55 253 physician CPG authors in the United States received personal and/or research payments from  
56 254 healthcare companies.<sup>46</sup> The higher proportion of CPG authors receiving payments in Japan can be  
57 255 attributed to the fact that most professional medical societies in Japan have implemented less  
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transparent COI policies. This is in line with our previous studies reporting on the matter.<sup>18 20</sup>

Furthermore, this investigation revealed that a select group of CPG authors, including the chairperson, received substantial personal payments from pharmaceutical companies. Only authors involved in writing the CPGs were mandated to declare their financial COIs, while other contributors did not publicly disclose any financial COIs with these companies. These results indicate that authors of Japanese CPGs for bipolar disorder and major depressive disorder clearly violate international COI policies on CPG development in several respects. The U.S. National Academy of Medicine's 2011 report and the Guidelines International Network advocate for a majority of CPG authors to be free from financial COIs.<sup>1 2</sup> These policies also stipulate that the chairperson of CPG development should not hold any COIs.<sup>1 2</sup> The Guideline Panel Review Working Group's criteria for red flags, as published in the British Medical Journal in 2013, indicate that financial COIs held by a CPG chairperson and multiple authors are significant concerns for the trustworthiness of the CPGs.<sup>47</sup> The prevalence of COIs exceeding 93% in this study is not a marginal discrepancy but a significant deviation from these standards, casting doubt on the objectivity and reliability of the guidelines.

Moreover, the study revealed that substantial payments were made by pharmaceutical companies marketing new antidepressants and sleep aids in Japan. For example, Sumitomo Pharma, the top payer, produces lurasidone (brand name: Latuda), which was approved for bipolar disorder and schizophrenia in 2020, and has been co-marketing venlafaxine hydrochloride (brand name: Effexor) with Pfizer Japan since 2018. MSD, another major payer, produces suvorexant (brand name: Belsomra), the world's first orexin receptor antagonist used for insomnia. Otsuka Pharmaceutical is known as one of the major manufacturers of atypical antipsychotics, such as aripiprazole (brand name: Abilify) and brexpiprazole (brand name: Rexulti), which are the most widely prescribed atypical antipsychotics in Japan.<sup>48</sup> Despite these financial ties between CPG authors and pharmaceutical companies manufacturing relevant drugs, the Japanese Society of Mood Disorders actively endorses adherence to these CPGs.<sup>49 50</sup> Given that the CPGs for bipolar disorder and major depressive disorder include pharmacotherapy recommendations that include medications from these companies, it is imperative that the close financial ties between CPG authors and the pharmaceutical industry be addressed. We strongly recommend the Japanese Society of Mood Disorders to enforce more transparent and stringent COI management strategies in the CPG development process for bipolar disorder and major depressive disorder to ensure the integrity and credibility of these guidelines.

### *Limitations*

This study is subject to several limitations. Primarily, the study focus on CPGs for bipolar disorder and major depressive disorder in Japan would limit the generalizability of our findings to other medical fields or countries. Additionally, the payment data were derived from a secondary source, the Medical Governance Research Institute's database, which contains payment information from member companies of the Japan Pharmaceutical Manufacturers Association for the period 2016-2020.<sup>27 51</sup> Absent legal mandates for precise payment disclosures in Japan, the potential for inaccuracies or underreporting in the database cannot be discounted. Furthermore, the voluntary nature of these disclosures means that financial interactions between CPG authors and non-disclosing pharmaceutical entities may remain undetected. Nevertheless, given that the member companies account for 80% of the market share for drugs and medical products in Japan,<sup>52</sup> the impact of financial relationships between the CPG authors and uncovered companies would be minimized.

### *Conclusions*

More than 93% of the authors of the Treatment Guidelines for Bipolar Disorder and Major

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3 305 Depressive Disorder developed by the Japanese Society of Mood Disorders received personal  
4 306 payments for the reimbursement of their lecturing, consulting, and writing activities from the  
5 307 pharmaceutical companies manufacturing related drugs. The total amounts of personal payments to  
6 308 the CPG authors were more than \$4.0 million over the five years. Nevertheless, the financial COIs  
7 309 were only declared by the limited group of CPG authors. Further transparent and rigorous COI  
8 310 management strategies must be warranted in the Japanese Society of Mood Disorders.  
9 311  
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11 312 **Author contribution:**  
12 313 A.M. contributed to data collection, resource, software, formal analysis, visualization, supervision,  
13 314 and study administration. All authors (A.M., H.K., and Y.S.) contributed to study conceptualization,  
14 315 methodology, writing the original draft, and reviewing the draft.  
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17 317 **Conflicts of interest:**  
18 318 The authors declare that there were no conflicts of interest for this study.  
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21 320 **Funding sources:**  
22 321 The authors declare that there were no funding sources for this study.  
23 322  
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25 324 **IRB Statement**  
26 325 As this study was a retrospective analysis of publicly available data and met the definition of non-  
27 326 human subjects research, no institutional board review and approval were required in accordance  
28 327 with the Japanese Ministry of Health, Labor, and Welfare’s Ethical Guidelines for Medical and  
29 328 Health Research Involving Human Subjects. This study followed the Strengthening the Reporting of  
30 329 Observational Studies in Epidemiology (STROBE) guideline.  
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33 331 **Declaration of generative AI in scientific writing**  
34 332 During the preparation of this work, the authors used ChatGPT version 4.0 solely for the purpose of  
35 333 identifying and correcting grammatical and spelling errors, and we did not use it for the creation of  
36 334 any intellectual parts of the manuscript. After using this tool, the authors carefully reviewed and  
37 335 edited the content as needed and take full responsibility for the content of the publication.  
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39 336  
40 337 **Data availability statement:**  
41 338 All data used in this study is available from Yen For Docs database run by Medical Governance  
42 339 Research Institute (<https://yenfordocs.jp/>) and each pharmaceutical companies belonging to the Japan  
43 340 Pharmaceutical Manufacturers Association. Due to privacy protection, payment data of individual  
44 341 CPG authors will be available from the corresponding author upon reasonable request.  
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46 342  
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51 347 the purpose of identifying and correcting grammatical and spelling errors, and we did not use it for  
52 348 the creation of any intellectual parts of the manuscript. After using this tool, the authors carefully  
53 349 reviewed and edited the content as needed and take full responsibility for the content of the  
54 350 publication.  
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Table 1. Summary of personal payments from pharmaceutical companies to psychiatry clinical practice guideline authors from 2016 to 2020

| Variables                                               | 2016                       | 2017                       | 2018                      | 2019                    | 2020                  | Four-year total<br>amounts from<br>2016 to 2019 | Five-year total<br>amounts from<br>2016 to 2020 |
|---------------------------------------------------------|----------------------------|----------------------------|---------------------------|-------------------------|-----------------------|-------------------------------------------------|-------------------------------------------------|
| Total amount of payments, \$                            | 959,289                    | 872,245                    | 769,649                   | 743,295                 | 697,110               | 3,344,478                                       | 4,041,648                                       |
| Mean payments per author<br>(standard deviation), \$    | 21,318<br>(27,281)         | 19,383<br>(24,380)         | 17,103<br>(24,797)        | 16,518<br>(21,363)      | 15,400<br>(22,363)    | 74,322 (93,767)                                 | 89,814 (111,760)                                |
| Median payments per author<br>(interquartile range), \$ | 11,992 (1,877<br>– 24,498) | 10,678 (2,309<br>– 25,058) | 5,452 (1,251 –<br>22,591) | 4,506 (834 –<br>26,830) | 2,701 (0 –<br>22,900) | 44,688 (9,325 –<br>93,393)                      | 51,403 (9,982 –<br>111,567)                     |
| Maximum payment amounts, \$                             | 120,927                    | 100,635                    | 114,153                   | 107,553                 | 94,330                | 411,745                                         | 506,108                                         |
| Authors receiving personal<br>payments (N=45), n (%)    |                            |                            |                           |                         |                       |                                                 |                                                 |
| Any payments                                            | 39 (86.7)                  | 41 (91.1)                  | 36 (80.0)                 | 37 (82.2)               | 34 (75.6)             | 42 (93.3)                                       | 42 (93.3)                                       |
| >\$10,000                                               | 24 (53.3)                  | 23 (51.1)                  | 20 (44.4)                 | 22 (48.9)               | 19 (41.7)             | 32 (71.1)                                       | 33 (73.3)                                       |
| >\$50,000                                               | 6 (13.3)                   | 5 (11.1)                   | 4 (8.9)                   | 2 (4.4)                 | 3 (6.7)               | 21 (46.7)                                       | 23 (51.1)                                       |
| >\$100,000                                              | 1 (2.2)                    | 1 (2.2)                    | 1 (2.2)                   | 1 (2.2)                 | 0 (0)                 | 10 (22.2)                                       | 15 (33.3)                                       |
| >\$250,000                                              | 0 (0)                      | 0 (0)                      | 0 (0)                     | 0 (0)                   | 0 (0)                 | 2 (4.4)                                         | 3 (6.7)                                         |

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



Table 2. Payment amounts by top 10 companies.

| Variables                                           | Payment amounts (%), \$ |                |                |                |                |                 | Major products used for bipolar and major depressive disorders (generic name)                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------|-------------------------|----------------|----------------|----------------|----------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                     | 2016                    | 2017           | 2018           | 2019           | 2020           | Overall         |                                                                                                                                                                                                                                                                                                                                                       |
| Total amounts of payments                           | 959,289 (100)           | 872,245 (100)  | 769,649 (100)  | 743,295 (100)  | 697,170 (100)  | 4,041,648 (100) |                                                                                                                                                                                                                                                                                                                                                       |
| Top 10 companies making the largest payment amounts |                         |                |                |                |                |                 |                                                                                                                                                                                                                                                                                                                                                       |
| Sumitomo Pharma                                     |                         |                |                |                |                | 695,031 (17.2)  | Lexor (venlafaxine, co-promotion with Pfizer Japan)<br>Erispan (fludiazepam)<br>Excegran (zonisamide)<br>Halomonth (haloperidol decanoate)<br>Mystan (clobazam)<br>Noritren (nortriptyline)<br>Landosen (clonazepam)<br>Latuda (lurasidone)<br>Lonasen Tapes (blonanserin)<br>Lullan (perospirone)<br>Sediel (tandospirone)<br>Serenace (haloperidol) |
| Eisai                                               | 180,436 (18.8)          | 105,531 (12.1) | 127,847 (16.6) | 106,975 (14.4) | 174,243 (25.0) | 408,323 (10.1)  | Dayvigo (lemborexant)<br>Spiriopitan spiperone)                                                                                                                                                                                                                                                                                                       |
| MSD                                                 | 45,779 (4.8)            | 78,418 (9.0)   | 52,244 (6.8)   | 80,026 (10.8)  | 151,856 (21.8) | 357,526 (8.8)   | Belsomra (suvorexant)<br>Remeron (mirtazapine)<br>Reslin (trazodone)<br>Tetramide (mianserin)                                                                                                                                                                                                                                                         |
| Otsuka Pharmaceutical                               | 122,880 (12.8)          | 83,528 (9.6)   | 79,420 (10.3)  | 57,679 (7.8)   | 14,020 (2.0)   | 354,638 (8.8)   | Abilify (aripiprazole)<br>Rexulti (brexpiprazole)                                                                                                                                                                                                                                                                                                     |
| Takeda Pharmaceutical                               | 64,794 (6.8)            | 73,028 (8.4)   | 64,161 (8.3)   | 86,679 (11.7)  | 65,976 (9.5)   | 337,370 (8.3)   | Depas (etizolam)<br>Eurodin (estazolam)<br>Trintellix (vortioxetine)                                                                                                                                                                                                                                                                                  |
| Pfizer Japan                                        | 69,017 (7.2)            | 78,990 (9.1)   | 45,019 (5.8)   | 71,206 (9.6)   | 73,138 (10.5)  | 311,571 (7.7)   | Amoxan (amoxapine)                                                                                                                                                                                                                                                                                                                                    |
|                                                     | 78,269 (8.2)            | 106,973        | 65,996 (8.6)   | 46,086 (6.2)   | 14,247 (2.0)   |                 |                                                                                                                                                                                                                                                                                                                                                       |

|                             |              |              |              |              |              |               |                                                                                                                                                  |
|-----------------------------|--------------|--------------|--------------|--------------|--------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |              | (12.3)       |              |              |              |               | Desyrel (trazodone)<br>Effexor (venlafaxin)<br>Halcion (triazolam)<br>Jzoloft (sertraline)<br>Wypax (lorazepam)<br>Mirtzapin (generic mirtzapin) |
| Mitsubishi Tanabe<br>Pharma | 58,501 (6.1) | 47,295 (5.4) | 61,056 (7.9) | 59,114 (8.0) | 25,789 (3.7) | 251,755 (6.2) | Clofekton (clocapramine hydrochloride)<br>Contomin (chlorpromazine)<br>Levotomin (levomepromazine)<br>Rize (clotiazepam)                         |
| Eli Lilly Japan             | 56,337 (5.9) | 60,899 (7.0) | 59,231 (7.7) | 36,314 (4.9) | 38,130 (5.5) | 250,910 (6.2) | Strattera (atomoxetine)<br>Zyprexa (olanzapine)<br>Zyprexa Zydis (olanzapine)                                                                    |
| Meiji Seika<br>Pharma       | 75,608 (7.9) | 53,110 (6.1) | 57,841 (7.5) | 27,228 (3.7) | 24,235 (3.5) | 238,023 (5.9) | Depromel (fluvoxamine)<br>Reflex (mirtazapine)<br>Sycrest (asenapine)<br>Aripiprazole (generic aripiprazole)                                     |
| Mochida<br>Pharmaceutical   | 35,768 (3.7) | 29,405 (3.4) | 31,597 (4.1) | 41,378 (5.6) | 17,209 (2.5) | 155,356 (3.8) | Lexapro (escitalopram)<br>Tecipul (setiptiline)<br>Zolpidem (generic zolpidem)                                                                   |



Table 3. Payments by author categories in the bipolar disorder and major depressive disorder clinical practice guidelines

| Variables                                                   | Guideline disease category |                           |
|-------------------------------------------------------------|----------------------------|---------------------------|
|                                                             | Bipolar disorder           | Major depressive disorder |
| Number of all authors, N                                    | 33                         | 42                        |
| Role of guideline authors, n (%)                            |                            |                           |
| Writing authors <sup>a</sup>                                | 4 (12.1)                   | 14 (33.3)                 |
| Supporting authors <sup>b</sup>                             | 5 (15.2)                   | 12 (28.6)                 |
| Guideline development committee authors <sup>c</sup>        | 24 (72.7)                  | 16 (38.1)                 |
| Payments by author roles                                    |                            |                           |
| Total payment amounts, \$                                   |                            |                           |
| Writing authors <sup>a</sup>                                | 532,717                    | 1,659,595                 |
| Supporting authors <sup>b</sup>                             | 12,140                     | 930,986                   |
| Guideline development committee authors <sup>c</sup>        | 2,548,718                  | 1,448,508                 |
| Number of authors receiving payments by author roles, n (%) |                            |                           |
| Writing authors <sup>a</sup>                                | 4 (100)                    | 14 (100)                  |
| Supporting authors <sup>b</sup>                             | 4 (80.0)                   | 10 (83.3)                 |
| Guideline development committee authors <sup>c</sup>        | 22 (91.7)                  | 16 (100)                  |
| Median payment amounts per author, \$                       |                            |                           |
| Writing authors <sup>a</sup>                                | 135,867 (78,553 – 187,806) | 87,610 (16,945 – 111,567) |
| Supporting authors <sup>b</sup>                             | 1,788 (715 – 1,845)        | 60,120 (1,573 – 142,732)  |
| Guideline development committee authors <sup>c</sup>        | 34,569 (11,588 – 184,068)  | 34,569 (14,331 – 149,624) |

<sup>a</sup> Writing authors directly contributed to the creation of guidelines.

<sup>b</sup> Supporting authors could have contributed to identifying relevant evidence and performing literature reviews.

<sup>c</sup> Guideline development committee authors were not directly involved in the creation of the guidelines, but critically reviewed the contents and recommendations of the initial guideline draft and revised them if necessary.

Table 4. Financial conflicts of interest self-declared by the guideline authors

| Variables                                                                                 | Bipolar disorder (N=4) | Major depressive disorder (N=14) |
|-------------------------------------------------------------------------------------------|------------------------|----------------------------------|
| Number of authors self-reporting conflicts of interest by category                        |                        |                                  |
| Speaking compensation                                                                     | 4 (100)                | 11 (78.6)                        |
| Scholarship donation                                                                      | 3 (75.0)               | 6 (42.9)                         |
| Consulting payments                                                                       | 0 (0)                  | 4 (28.6)                         |
| Collaborative research funds                                                              | 1 (25.0)               | 2 (14.3)                         |
| Advisory board                                                                            | 2 (50.0)               | 1 (7.1)                          |
| Contracted research funds                                                                 | 1 (25.0)               | 0 (0)                            |
| Any category                                                                              | 4 (100)                | 12 (85.7)                        |
| Industry-reported payments to authors                                                     |                        |                                  |
| Number of writing authors receiving payments from 2016 to 2020 by payment category, n (%) |                        |                                  |
| Lecturing payments                                                                        | 4 (100)                | 14 (100)                         |
| Consulting payments                                                                       | 4 (100)                | 12 (85.7)                        |
| Writing payments                                                                          | 4 (100)                | 9 (64.3)                         |
| Any payment category                                                                      | 4 (100)                | 14 (100)                         |
| Total payment amounts to writing authors from 2016 to 2020, \$                            |                        |                                  |
| Lecturing payments                                                                        | 399,929                | 1,073,071                        |
| Consulting payments                                                                       | 101,805                | 430,660                          |
| Writing payments                                                                          | 30,983                 | 155,864                          |

Legends: Proportion of authors reporting conflicts of interest were number of authors reporting conflicts of interest to the total number of writing authors.

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## STROBE Statement—checklist of items that should be included in reports of observational studies

|                           | Item No. | Recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Page No. | Relevant text from manuscript |
|---------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------------|
| <b>Title and abstract</b> | 1        | (a) Indicate the study's design with a commonly used term in the title or the abstract<br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |          |                               |
| <b>Introduction</b>       |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |                               |
| Background/rationale      | 2        | Explain the scientific background and rationale for the investigation being reported                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |          |                               |
| Objectives                | 3        | State specific objectives, including any prespecified hypotheses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |
| <b>Methods</b>            |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |                               |
| Study design              | 4        | Present key elements of study design early in the paper                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |          |                               |
| Setting                   | 5        | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |                               |
| Participants              | 6        | (a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br><i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br><i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants<br>(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed<br><i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case |          |                               |
| Variables                 | 7        | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |          |                               |
| Data sources/measurement  | 8*       | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 4        |                               |
| Bias                      | 9        | Describe any efforts to address potential sources of bias                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | n/a      |                               |
| Study size                | 10       | Explain how the study size was arrived at                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 3        |                               |

Continued on next page

|                        |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
|------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Quantitative variables | 11  | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why                                                                                                                                                                                                                                                                                                                                                                                                                                      |            |
| Statistical methods    | 12  | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed<br><i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed<br><i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses |            |
| <b>Results</b>         |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            |
| Participants           | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram                                                                                                                                                                                                                                                                   |            |
| Descriptive data       | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)                                                                                                                                                                                                                                               |            |
| Outcome data           | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time<br><i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure<br><i>Cross-sectional study</i> —Report numbers of outcome events or summary measures                                                                                                                                                                                                                                                                                 |            |
| Main results           | 16  | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period                                                                                                                                                     | 5-6<br>n/a |

Continued on next page

|                          |    |                                                                                                                                                                            |
|--------------------------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other analyses           | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses                                                                             |
| <b>Discussion</b>        |    |                                                                                                                                                                            |
| Key results              | 18 | Summarise key results with reference to study objectives                                                                                                                   |
| Limitations              | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias                 |
| Interpretation           | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability         | 21 | Discuss the generalisability (external validity) of the study results                                                                                                      |
| <b>Other information</b> |    |                                                                                                                                                                            |
| Funding                  | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based              |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).