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Changes in psychotropic polypharmacy and high-potency prescription following policy change: Findings from a large scale Japanese claims database

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Dear editor,

Psychotropic polypharmacy and long-term benzodiazepine receptor agonist (BzRA) use are major health issues as they can increase the risk of adverse effects. To promote the appropriate use of psychotropic drugs in Japan, medical fee reductions were implemented four times between 2012 and 2018 (Table S1).[1]

This observational study aimed to evaluate the effect of medical fee revisions on the polypharmacy and prescription of high-potency psychotropics by distinguishing between before and after intervention periods using a Japan Medical Data Center (JMDC) dataset containing all medical fee data of health insurance service subscribers aged 0–74 years (workers and their family members) (Table S2). Medical information of health insurance service subscribers who visited any department of a medical institution (hospitals, clinics, etc.) every April from 2005 to 2019 and were prescribed psychotropic drugs was extracted. Dosages of sulpiride <300 and ≥300 mg/day were considered antidepressant and antipsychotic dosages, respectively. The potency of psychotropics was calculated based on the psychotropic dose equivalence in Japan.[2] Drugs not listed in the psychotropic dose equivalence in Japan were defined as follows: flunitrazepam 1 mg/day = suvorexant 20 mg/day = ramelteon 8 mg/day and chlorpromazine 100 mg/day = asenapine 2.5 mg/day = brexpiprazole 0.5 mg/day (Table S3). The proportion of

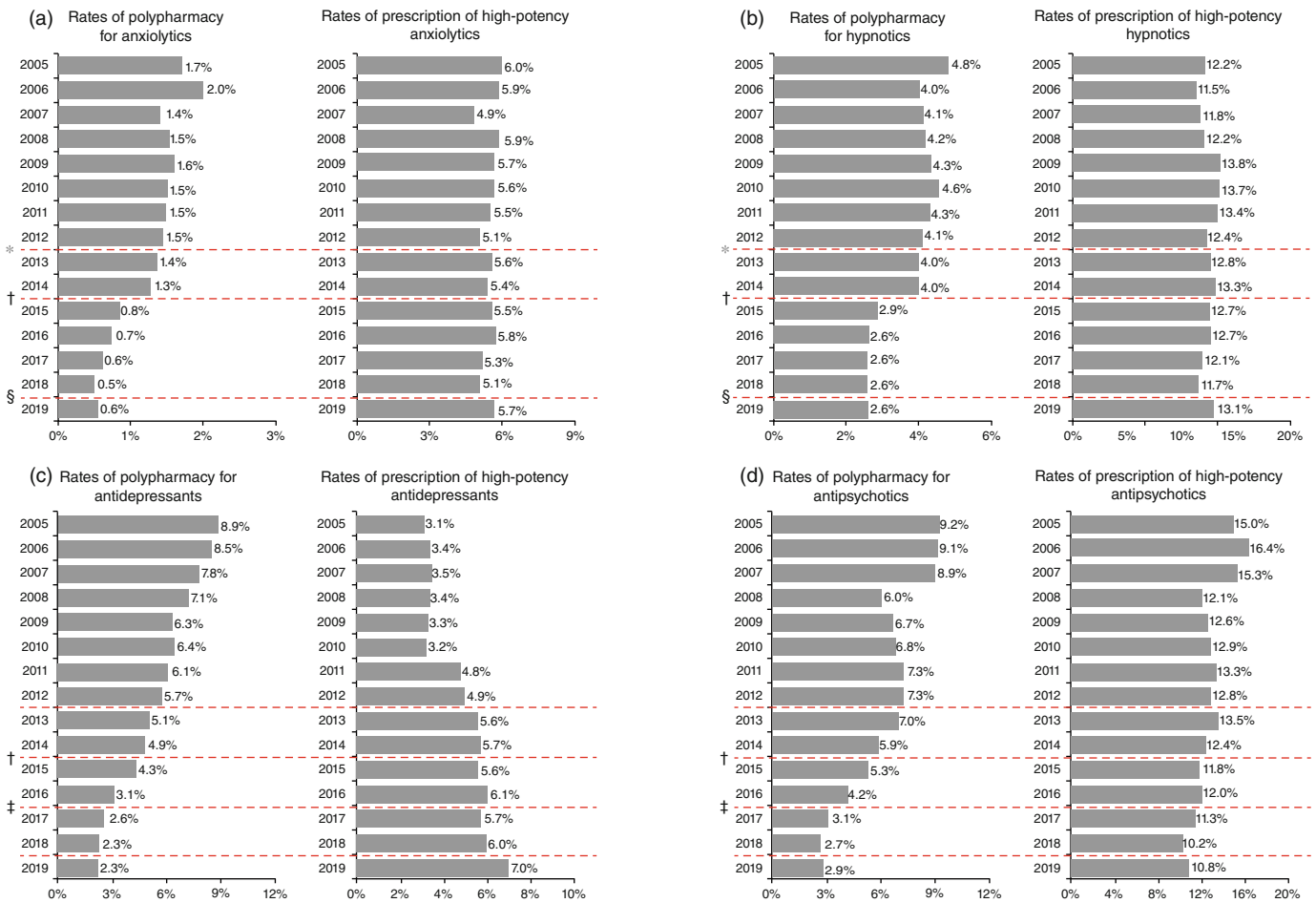

Fig. 1 Patients prescribed three or more drugs and those prescribed high-potency psychotropic drugs, including (a) anxiolytics, (b) hypnotics, (c) antidepressants, and (d) antipsychotics. Based on the census data, the rates of polypharmacy and prescription of high-potency psychotropic drugs were adjusted for age based on 5-year age groups and sex. The figure on the left shows the proportion of subscribers who were prescribed three or more of each class of psychotropic drugs among subscribers who were prescribed psychotropic drugs every April between 2005 and 2019. The figure on the right shows the proportion of subscribers prescribed high-potency psychotropic drugs among subscribers prescribed psychotropic drugs. High-potency anxiolytics, hypnotics, antidepressants, and antipsychotics were defined as those equivalent to >15 mg/day diazepam, >2 mg/day flunitrazepam, >300 mg/day imipramine, and >600 mg/day chlorpromazine, respectively. †Revision in 2012. ‡Revision in 2014. §Revision in 2016. ¶Revision in 2018.

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patients prescribed three or more psychotropics—such as anxiolytics, hypnotics, antidepressants, and antipsychotics—(polypharmacy rate) among the total number of prescribed psychotropics was calculated. Subsequently, the proportions of those prescribed high-potency psychotropics among those prescribed psychotropics (rate of prescription of high-potency psychotropics) were calculated. High-potency anxiolytics, hypnotics, antidepressants, and antipsychotics were defined as those equivalent to >15 mg/day diazepam, >2 mg/day flunitrazepam, >300 mg/day imipramine, and >600 mg/day chlorpromazine, respectively. The rates of polypharmacy and prescription of high-potency psychotropics were adjusted using the Japanese annual vital statistics. We set as benchmarks a reduction in the rates of the polypharmacy and prescriptions of high-potency psychotropics to qualify the intervention as beneficial.

This study was approved by the Ethics Committee of Akita University Graduate School of Medicine (approval number: 2352). The study was conducted per the ethical principles of the Declaration of Helsinki as revised in 1989 and the International Conference on Harmonization Guideline for Good Clinical Practice. As we analyzed an anonymized dataset, informed consent was waived.

Figure 1 shows changes in the rates of polypharmacy and prescription of high-potency psychotropics every April from 2005 to 2019 (Tables S4–S8, Figs S1–S5). Rates of polypharmacy of all four psychotropics were considered to have decreased. However, the polypharmacy rates of anxiolytics and hypnotics from 2015 onward and antidepressants and antipsychotics from 2017 onward remained stable. In contrast, the rates of prescription of high-potency antipsychotics decreased, those of anxiolytics and hypnotics remained generally unchanged, and those of antidepressants increased.

It is difficult to reduce the prescribed dosage or discontinue the use of BzRAs, the most frequently prescribed anxiolytics and hypnotics, due to physical dependence.[3] Patients who do not successfully reduce or discontinue BzRAs may require health policy and medical intervention. Cognitive-behavioral therapy (CBT) may be considered in patients with anxiety disorders who cannot reduce or discontinue anxiolytic use; CBT promotes the discontinuation of both short and long-term anxiolytic use.[4] In contrast, CBT for insomnia facilitates the short-term discontinuation of benzodiazepines; however, the effects may not last long.[5] Therefore, new long-term effective treatments for discontinuing hypnotics in patients with insomnia are required. Throughout the study period, polypharmacy rates decreased for antidepressants, whereas the rates of prescription of high-potency psychotropics increased annually. Although guidelines recommend that antidepressants be prescribed as monotherapy when treating depression,[6,7] patients suffering from depression failed to achieve remission with antidepressant monotherapy.[8] The increased rates of prescription of high-potency antidepressants in this study may be due to combination therapy of antidepressants for patients who did not achieve remission with antidepressant monotherapy. Rates of polypharmacy and prescription of high-potency antipsychotics decreased over time. Schizophrenia treatment guidelines recommend using antipsychotic monotherapy, possibly promoting appropriate antipsychotic use.[9,10]

There were some limitations. First, it is unclear to what extent the JMDC dataset represents the general Japanese population. Also, this study could not exclude other societal factors, besides medical fee revisions, that might have influenced psychotropic prescribing during the study period.

In conclusion, our results indicate that medical fee revision significantly reduced the polypharmacy rates for all psychotropic drugs. However, fee revision did not reduce the prescription rates of high-potency psychotropics other than antipsychotics. Further studies examining the effects of medical fee revisions for reducing long-term BzRAs use are warranted.

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Disclosure statement

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Trends in the rates of polypharmacy and prescription of high-potency anxiolytics over time.

Fig. S2 Trends in the rates of polypharmacy and prescription of high-potency hypnotics over time.

Fig. S3 Trends in the rates of polypharmacy and prescription of high-potency antidepressants over time.

Fig. S4 Trends in the rates of polypharmacy and prescription of high-potency antipsychotics over time.

Fig. S5 Trends in the monthly prescription rates of psychotropic drugs over time.

Table S1 Details of the medical fee revisions to reduce psychotropic polypharmacy and long-term use of benzodiazepine receptor agonists in Japan.

Table S2 Demographic data of the subscribers to the health insurance service.

Table S3 List of the psychotropic drugs that can be prescribed in Japan and their potencies.

Table S4 Prescription of concomitant psychotropic drugs.

Table S5 The proportion of those prescribed three or more psychotropic drugs among subscribers to the health insurance service who were prescribed psychotropic drugs (by 5-year age group and sex).

Table S6 Potency of psychotropics.

Table S7 The proportion of those prescribed high-potency psychotropics among subscribers to the health insurance service who were prescribed psychotropic drugs (by 5-year age group and sex).

Table S8 Monthly prescription rate of psychotropics (by 5-year age group and sex).

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A case of Wernicke's encephalopathy that maintains long-term cognitive deterioration but not inflammation in spite of thiamine supplementation

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Wernicke's encephalopathy (WE) is an acute neuropsychiatric syndrome mainly associated with an alcohol use disorder and/or malnutrition that courses with neuroinflammation and cognitive impairment caused by vitamin B1 deficit. This condition is reversible when the patient is supplemented with thiamine. However, the evolution of the impairment by cognitive domains and the progression of the inflammation in the long term have never been described.

Herein, we present the case of a 47-year-old White woman, medium socioeducational level, smoker, with a history of alcohol consumption who was diagnosed with WE in the absence of malnutrition following Caine *et al*. operational criteria[1] and cranial magnetic resonance imaging findings (see supporting information). She attended emergency services for impaired vision (binocular diplopia), marked restriction of horizontal eye movements, gait instability, and mnesic impairments. She reported finishing the school term without difficulties. She (and her family) ruled out any previous head trauma, neurological or cognitive problems, being this the first time with subjective memory complaints. A diagnosis of Korsakoff syndrome was ruled out since the patient did not have its hallmark symptom of anterograde amnesia.[2] A high dose of intravenous thiamine (500 mg/8 h) was prescribed during 4 days, together with B/C vitamin complexes, tiapride and disulfiram, switching to an oral thiamine guideline (100 mg/24 h) for 6 months (disulfiram was also maintained during this period).

After the initial days in the emergency service, she was referred to the hospital outpatient alcohol program of the Addictive Behavior and Dual Pathology Unit (Psychiatry Department) to maintain abstinence. Then, a broad and comprehensive neuropsychological assessment was performed 5 weeks ($t = 0$) and 6 months ($t = 1$) after, evaluating the following neuropsychological domains: general cognitive functioning, visuospatial ability, memory/learning, executive functions, and language and processing speed. Blood samples were also collected at these time points to study key inflammatory markers such as the presence of lipopolysaccharide and its binding protein (lipopolysaccharide binding protein [LBP]) in plasma (Methods in supporting information).

Initially ($t = 0$), the patient presented with marked general cognitive functioning deterioration, as expected (altered mental status and consciousness, confusion, and disorientation).[1] Memory was the most affected domain, and visuospatial ability, executive functions, and processing speed were also severely impaired. However, language was shown to be the least affected domain (indeed, some aspects of language remained preserved). Our patient brought to light the great difficulty in returning the impaired cognitive domains to normal in spite of thiamine supplementation, since all domains, despite some improvement, showed deficits at $t = 1$ with the exception of executive functions, which were shown to be the domain with the highest resistance to recovery (see supporting information).

We found high blood levels of lipopolysaccharide in our patient at $t = 0$ (41 pg/mL), increased in 67% compared with age- and sex-matched controls (13.5 ± 0.01 pg/mL; $n = 4$). The levels were decreased (16 pg/mL) at $t = 1$, reaching similar values than controls. The same pattern was observed by analysis of the LBP plasma levels (a molecule needed for the lipopolysaccharide signaling),[3] which were increased around 45% (34.85 μg/mL) versus controls (19.28 ± 5.45 μg/mL; $n = 4$) at $t = 0$ and decreased to similar levels than controls (17.94 μg/mL) at $t = 1$ follow-up. The high inflammatory response at $t = 0$ could be associated with the initial cognitive impairment, as suggested in other studies.[4,5] However, the persistence of cognitive impairment at $t = 1$ did not match with the recovery in the inflammatory status of the patient. Indeed, after 6 months of acute WE symptoms, and under thiamine treatment, the general inflammatory condition improved, whereas the cognitive impairment persisted, with no evolution to Korsakoff syndrome, pointing out the great difficulty of cognitive processes to return to normal once impairment has occurred.

This case report highlights the importance of conducting a full and comprehensive cognitive assessment in patients with WE as it can be associated with severe and persistent cognitive impairment manifested in a wide range of specific cognitive domains, in spite of the thiamine supplementation. Lipopolysaccharide and LBP (proinflammatory markers) could be highly activated in WE and could be useful risk biomarkers to identify early states of the pathology, since they decrease in the long term.