Central Nervous System Agent Classes and Fragility Fracture Risk among Elderly Japanese Individuals in a Nationwide Case-Crossover Design Study

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fracture (Fig. 1). We thought that a 30-d length would be a suitable washout period to avoid carryover effects from the control window to the case window, and to minimize changes in patient conditions, such as frailty and disease severity. Effects of extended length of case and control windows were evaluated as sensitivity analyses by changing the length from 3 to 5, 10, and 15 d.

NDB Japan, which is the data source of the present study, includes almost all Japanese citizens (total of approximately 125 million citizens and approximately 31 million elderly people [aged ≥65 years]), of which claims data from April 2012 to September 2014 were used in the present study. The study population met the following inclusion criteria: (1) opioid non-users with any medication record who had incurred fragility fractures in the proximal humerus, distal radius, vertebra, and/or femoral neck at age of 65 years or over from May 2013 to September 2014 and (2) those who had not been hospitalized for at least 13 months prior to the occurrence of the fracture.

The occurrence of fragility fractures, which are caused by a slight external force such as falling from a standing height or less,4,20 was determined by (1) use of diagnostic codes and modifier codes added to the diagnostic codes and (2) radiographic examination on the date of diagnosis at the institution where the diagnosis was made. The combinations of diagnostic codes and modifier codes defined as fragility fractures are shown in Supplementary Materials Table S1. Fracture diagnoses with the following modifier codes were not recognized as fragility fractures: modifier codes that were not thought as fracture occurrence (e.g. 5124; old) or fragility fractures (e.g. 1002: axilla) (Supplementary materials Table S2).

**Medication** All prescribed medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system of WHO. Medications not included in the ATC list were classified into similar ATC classification groups. CNS agent classes were defined as antiepileptic agents (ATC code N03A), anti-Parkinson agents (N04), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), and anti-dementia agents (N06D).

We addressed bone metabolism-related agents and fall-inducing agents as potential confounding medications. Bone metabolism-related agents were classified as the following 12 groups: proton pump inhibitors, steroids, thyroid hormones, antiestrogens, vitamin D agents, calcium agents, anabolic steroids, vitamin K agents, statins, estrogen agonists, calcium homeostasis agents and somatropin, and bisphosphonates and receptor activator of nuclear factor-kappa B ligand-targeted antibody. Fall-inducing agents were classified as the following eight groups: insulins, hypoglycemic agents except for insulin, nitrates and erectile dysfunction agents, antiadrenergic agents and vasodilators relaxing vascular smooth muscle, diuretics, beta-blocking agents, calcium channel blockers, and renin-angiotensin-system-acting agents. The detailed definition has been published elsewhere.17)

For the above medications, oral formulations, transdermal absorption agents with systemic effects (rotigotine, rivastigmine, estrogen, nitrates, and beta-blocking agents), and injection formulations were employed. The dates that oral formulations would have been used were identified as day-units using the dispensing date and days-of-supply. The administration days for transdermal absorption agents were estimated by dividing the total quantity by the standard daily maintenance dose. The dates that injection formulations would have been used were defined as only the dispensing dates, excluding self-injection agents such as insulin and glucagon-like peptide-1. The dates for self-injection were defined as 365 d.

**Statistical Analyses** The usage pattern of CNS agent classes between case and control windows was investigated, because discordant data of medication use between windows (i.e., a class used in the case window but not in control windows and vice versa), not concordant data, are used for estimation of odds ratios (ORs) in the case-crossover design.21 Conditional logistic regression analyses for 1:3 matched sets estimated crude and adjusted ORs of CNS agent classes for fragility fracture. Crude ORs were also estimated with the Cochran–Mantel–Haenszel (CMH) method, because the ORs estimated from conditional logistic regression analyses are likely to be biased due to within-subject exposure dependence,22 which is natural for a case-crossover design of self-control.

CNS agents, especially anxiolytics, hypnotics, and sedatives, are often prescribed as medications to be taken as needed according to physicians’ direction (pro re nata). Data for pro re nata CNS agents (PRN-CNS agents) were thought to influence the estimation of ORs, as dates when patients actually used PRN-CNS agents were unclear. We therefore estimated the ORs for both groups, including or excluding patients to whom PRN-CNS agents were dispensed in the case window or control windows (PRN-CNS agent users). PRN use was defined with the PRN code that was described as the medication record in medical claims and as the prescription base record in dispensing claims.

Statistical significance was assessed with 95% confidence intervals (CIs). SAS Enterprise Guide 7.13 and SAS ver.9.4 (SAS Institute Inc., Cary, NC, U.S.A.) were used for data processing and statistical analyses.

**RESULTS**

A total of 446101 patients who met the inclusion crite-
Fragility fractures is illustrated elsewhere.\textsuperscript{16} Increased (were able to be interpreted as almost the same), ied (Table 4). The adjusted ORs of antipsychotics were slightly classes in both groups, but the magnitude of the increase var-
longer-length windows had increased adjusted ORs for all
the same values for all CNS agent classes.

The adjusted ORs from conditional logistic regression showed almost
statistically significant classes (e.g. antiepileptic agents,
leptic agents (\textit{as needed}). The adjusted OR of antiepileptic agents for fragility frac-
ture risk of antiepileptic agents\textsuperscript{8} and showed a relative risk
(RR) of 2.0 for cohort studies and 1.8 for case-control studies.
A meta-analysis by Takkouche et al.\textsuperscript{3} showed a
RR of 1.5 for non-barbiturates and 2.2 for barbiturates. Shiek
et al. reported that fractures occurred more often during treat-
ment with antiepileptic agents in patients without vs. with
seizures.\textsuperscript{23} Involvement of low bone mineral density from
antiepileptic agent-mediated hepatic enzyme induction\textsuperscript{8,24}
and drowsiness related to use of antiepileptic agents\textsuperscript{8} are reported as
the underlying mechanisms. In the present study, the exis-
tence of seizure prior to the occurrence of fragility fractures
was unclear, but percentage of elderly individuals who used

Sensitivity analysis for length of windows showed that the
discordant use: 0.9% use in the case window but non-use
in the control windows and 0.5% non-use in the case window
but use in the control windows if including PRN-CNS agent
users, and 0.5 and 0.3%, respectively, if excluding PRN-CNS
agent users.

The adjusted OR of antiepileptic agents for fragility frac-
ture was 2.40 (95% CI, 2.28–2.53) if including PRN-CNS
agent users and 2.59 (2.39–2.80) if excluding PRN-CNS agent
users, being the highest among CNS agent classes (Table 3,
Fig. 3). The following classes with adjusted ORs of approxi-
ately 1.0 to 1.5 were anti-dementia agents, antipsychotics,
anti-Parkinson agents, and antidepressants. Of them, anti-
deementia agents and antipsychotics showed slightly higher
ORs: 1.54 (1.46–1.63) for anti-dementia agents if including
PRN-CNS agent users and 1.48 (1.37–1.59) if excluding them,
and 1.47 (1.37–1.57) for antipsychotics if including PRN-CNS
agent users and 1.52 (1.37–1.69) if excluding them. The ad-
justed ORs of hypnotics and sedatives and anxiolytics were
not statistically significant for either group.

Compared with the crude ORs of logistic regression, those
estimated with the CMH method were lower, especially for
CNS agent classes with relatively greater ORs such as antiepi-
leptic agents (e.g. 1.74 vs. 2.45 for antiepileptic agents includ-
ing PRN-CNS agent users), but statistically significant classes
were the same with methods (Table 3). Crude ORs and ad-
justed ORs from conditional logistic regression showed almost
the same values for all CNS agent classes.

Sensitivity analysis for length of windows showed that the
longer-length windows had increased adjusted ORs for all
classes in both groups, but the magnitude of the increase var-
ied (Table 4). The adjusted ORs of antipsychotics were slightly
increased (were able to be interpreted as almost the same),
compared with antiepileptic agents, anti-dementia agents,
anti-Parkinson agents, and antidepressants. Hypnotics and
sedatives and anxiolytics were not associated with fragility
fractures for the 3-d window, but a slightly significant associa-
tion was found for the 15-d window.

DISCUSSION

This case-crossover design study found that antiepileptic agents had the highest risk of fragility fracture among the wide range of CNS agent classes prescribed to relatively healthy elderly people in Japan, who were opioid non-users without hospitalization for at least 13 months. The OR for fragility fractures was approximately 2.0 for antiepileptic agents (adjusted OR of 2.40 from conditional logistic regression and crude OR of 1.74 from CMH). The ORs were approximately 1.0 to 1.5 for anti-dementia agents, antipsychotics, anti-
Parkinson agents, and antidepressants, although the two former classes showed slightly higher ORs than the rest.

The results were relatively consistent, even if the use of PNR-CNS agents and length of windows were taken into account. Besides, the estimated fracture risk was almost the same as in previous studies, especially for antiepileptic agents, antipsychotics, and antidepressants, as described below. Use of the NDB Japan, which includes approximately 31 million elderly individuals aged \( \geq 65 \) years in Japan, enabled estimation of the risk of a wide range of CNS agents with sufficient statistical power and generalization of the findings. Elderly individuals in Japan who use antiepileptic agents and combinations of antiepileptic agents and CNS agent classes with the next-highest ORs should be carefully monitored.

A meta-analysis by Shen et al.\textsuperscript{2} in 2014 estimated the fracture risk of antiepileptic agents\textsuperscript{8} and showed a relative risk (RR) of 2.0 for cohort studies and 1.8 for case-control studies. Another meta-analysis by Takkouche et al. in 2007\textsuperscript{3} showed a RR of 1.5 for non-barbiturates and 2.2 for barbiturates. Shiek et al. reported that fractures occurred more often during treat-
mant with antiepileptic agents in patients without vs. with

The detailed flowchart to identify patients who incurred fragility fractures is illustrated elsewhere.\textsuperscript{16}
antiepileptic agents in the case window (i.e., immediately before incurring the fracture) but did not use them in the control windows was certainly higher than the opposite pattern, suggesting that the use of antiepileptic agents, not the occurrence of seizures, caused fragility fractures. This is because an antiepileptic agent would have been used after a fracture if a seizure caused the fracture.

Regarding antipsychotics and antidepressants, several previous cohort, case-control, and meta-analysis studies support the findings of the present study: a RR of 1.6\textsuperscript{3} and a hazard ratio (HR) of 1.4\textsuperscript{5} for antipsychotics (OR of 1.7 for first-generation antipsychotics and 1.3 for second-generation antipsychotics\textsuperscript{9}) and a RR of 1.6 for antidepressants\textsuperscript{3} (1.7 for selective serotonin reuptake inhibitors (SSRIs)),\textsuperscript{10,11} a HR of 1.7 for SSRIs and serotonin and noradrenaline reuptake inhibitors,\textsuperscript{12} and a RR of 1.5\textsuperscript{13} or a nonsignificant HR\textsuperscript{5} for tricyclic antidepressants. In addition, the case-crossover design study by Leach \textit{et al.}\textsuperscript{4} also showed an OR of 1.5 each for antipsychotics and SSRIs.

The use of medications such as SSRIs,\textsuperscript{5,11,12} antipsychot-
ics,\(^5\) and high doses of levodopa\(^25\) was reported to be an independent risk factor for fracture, but some reports showed an association between mental and nervous system disorders and fracture risk; depressive disorder\(^26,27\) and Parkinson's disease\(^28\) have been associated with decreased bone mineral density, and Parkinson's disease\(^25,29\) and Alzheimer's disease\(^30,31\) have been associated with increased fracture risk.

Therefore, as described below, we think that it is difficult to exclude the possibility of confounding completely due to the disease requiring a prescription (called 'confounding by indication') from the findings of the present study.

The results of the present study showed that the risk of fragility fracture associated with the use of hypnotics and anxiolytics was statistically nonsignificant for the analyses with a 3-d window, but marginally significant in analyses with longer windows. Results of previous studies are controversial; the association was nonsignificant in the meta-analysis by Takkouche et al.\(^3\) and in a case-crossover study by Leach et al.,\(^4\) and the RR was 1.5\(^14\) and 1.2\(^15\) in two other meta-analyses.

The present study has some limitations related to the case-crossover design. First, the findings may have been related to the disease requiring a prescription (called 'confounding by indication') from the findings of the present study.

Table 2. Usage Pattern of CNS Agent Classes between Case and Control Windows

<table>
<thead>
<tr>
<th>Class</th>
<th>Case window vs. Control windows(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use vs. Use n (%)(^b)</td>
</tr>
<tr>
<td>Including PRN-CNS agent users, n = 446101</td>
<td></td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>50398 (3.8)</td>
</tr>
<tr>
<td>Anti-dementia agents</td>
<td>103066 (7.7)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>52021 (3.9)</td>
</tr>
<tr>
<td>Anti-Parkinson agents</td>
<td>31757 (2.4)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>54938 (4.1)</td>
</tr>
<tr>
<td>Hypnotics and sedatives</td>
<td>166388 (12.4)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>146366 (10.9)</td>
</tr>
</tbody>
</table>

Excluding PRN-CNS agent users, n = 352828

<table>
<thead>
<tr>
<th>Class</th>
<th>Use vs. Use n (%)(^b)</th>
<th>Use vs. Non-use n (%)(^b)</th>
<th>Non-use vs. Use n (%)(^b)</th>
<th>Non-use vs. Non-use n (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic agents</td>
<td>21769 (2.1)</td>
<td>5525 (0.5)</td>
<td>3044 (0.3)</td>
<td>1028146 (97.1)</td>
</tr>
<tr>
<td>Anti-dementia agents</td>
<td>49204 (4.7)</td>
<td>4802 (0.5)</td>
<td>3697 (0.4)</td>
<td>1000781 (94.6)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>19981 (1.9)</td>
<td>2696 (0.3)</td>
<td>1960 (0.2)</td>
<td>1033847 (97.7)</td>
</tr>
<tr>
<td>Anti-Parkinson agents</td>
<td>13647 (1.3)</td>
<td>996 (0.1)</td>
<td>781 (0.1)</td>
<td>1043060 (98.5)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>20888 (2.0)</td>
<td>2065 (0.2)</td>
<td>1736 (0.2)</td>
<td>1033795 (97.7)</td>
</tr>
<tr>
<td>Hypnotics and sedatives</td>
<td>69922 (6.6)</td>
<td>12512 (1.2)</td>
<td>12241 (1.2)</td>
<td>963809 (91.1)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>62951 (6.0)</td>
<td>9022 (0.9)</td>
<td>9020 (0.9)</td>
<td>977491 (92.4)</td>
</tr>
</tbody>
</table>

CNS central nervous system; PRN, pro re nata (as needed). \(^a\) Use of CNS agent classes in control windows was defined as ‘use’ if they were used in either window of three control windows. \(^b\) Number of combination of case window and each control window was 1338303 for a group including PRN-CNS agent users and 1058484 for a group excluding those because it was calculated by multiplying three (number of control windows) by number of patients. The percentages were estimated by dividing the number identified as each use pattern by 1338303 for a group including PRN-CNS agent users or 1058484 for a group excluding those.

Table 3. Crude and Adjusted ORs of CNS Agent Classes for Fragility Fracture

<table>
<thead>
<tr>
<th>Class</th>
<th>Logistic regression</th>
<th>CMH</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)(^a)</td>
</tr>
<tr>
<td>Including PRN-CNS agent users, n = 446101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>2.45 (2.33, 2.59)</td>
<td>2.40 (2.28, 2.53)</td>
</tr>
<tr>
<td>Anti-dementia agents</td>
<td>1.57 (1.48, 1.65)</td>
<td>1.54 (1.46, 1.63)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1.59 (1.49, 1.70)</td>
<td>1.47 (1.37, 1.57)</td>
</tr>
<tr>
<td>Anti-Parkinson agents</td>
<td>1.52 (1.35, 1.71)</td>
<td>1.32 (1.18, 1.49)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.25 (1.17, 1.34)</td>
<td>1.13 (1.06, 1.22)</td>
</tr>
<tr>
<td>Hypnotics and sedatives</td>
<td>1.03 (1.00, 1.06)</td>
<td>1.01 (0.99, 1.04)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>1.02 (0.99, 1.06)</td>
<td>1.00 (0.96, 1.03)</td>
</tr>
</tbody>
</table>

Excluding PRN-CNS agent users, n = 352828

<table>
<thead>
<tr>
<th>Class</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)(^a)</th>
<th>Crude OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic agents</td>
<td>2.66 (2.46, 2.87)</td>
<td>2.59 (2.39, 2.80)</td>
<td>1.82 (1.71,1.93)</td>
</tr>
<tr>
<td>Anti-dementia agents</td>
<td>1.50 (1.39, 1.62)</td>
<td>1.48 (1.37, 1.59)</td>
<td>1.30 (1.22,1.38)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1.67 (1.50, 1.85)</td>
<td>1.52 (1.37, 1.69)</td>
<td>1.38 (1.27,1.49)</td>
</tr>
<tr>
<td>Anti-Parkinson agents</td>
<td>1.48 (1.25, 1.75)</td>
<td>1.28 (1.08, 1.52)</td>
<td>1.28 (1.12,1.46)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.32 (1.17, 1.48)</td>
<td>1.19 (1.06, 1.33)</td>
<td>1.19 (1.09,1.30)</td>
</tr>
<tr>
<td>Hypnotics and sedatives</td>
<td>1.04 (0.99, 1.08)</td>
<td>1.02 (0.98, 1.07)</td>
<td>1.02 (0.99,1.06)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>1.00 (0.95, 1.05)</td>
<td>0.97 (0.92, 1.02)</td>
<td>1.00 (0.96,1.04)</td>
</tr>
</tbody>
</table>

CNS, central nervous system; CMH, Cochran–Mantel–Haenszel; PRN, pro re nata (as needed); OR, odds ratio; CI, confidence interval. \(^a\) Adjusted for all CNS agent classes listed in this table and the pre-defined potential confounding medication groups of 12 groups of bone metabolism-related agents and 8 groups of fall-induced agents.
disease that developed immediately prior to fracture (time-variant confounders). Thus, confounding may have existed due to the disease requiring a prescription (called ‘confounding by indication’), as described above. However, the case-crossover design has the advantage that it can control time-invariant confounders, even if they are measurable, unmeasurable, or unknown: e.g. underlying diseases, complications, bone mineral density, daily supplements, alcohol, and smoking, and genetic factors in drug metabolism; therefore, it is less likely to be influenced by confounders than are cohort and case-control studies.

Second, due to persistent user bias\(^{(22)}\) that occurs with chronic, long-term medication use, the fragility fracture risk might have been overestimated; therefore, a cautious interpretation of the findings is needed. As chronic medications are permanently used after treatment start, a pattern of medication use in the case window and non-use in the control windows is more likely to occur than the opposite pattern, which causes overestimation. Such a chronic medication use pattern would also be more likely to occur if analyzed with extended window length, as the probability of non-use in the control windows becomes higher. Actually, the sensitivity analyses in the present study showed that longer windows caused an increase in the ORs for fragility fracture for antiepileptic agents, anti-dementia agents, anti-Parkinson agents, and antidepressants, but made the OR for antipsychotics almost even. The reason is presumably that the four former classes were permanently used once treatment started, but antipsychotics were used for a short period in elderly people, as medications for managing hallucinations, delusions and agitation along with dementia.\(^{(33–35)}\)

Third, there is within-subject exposure dependency\(^{(22)}\) by using conditional logistic regression in case-crossover design, causing overestimation of risk. For this issue, the present study estimated crude ORs for fragility fracture using the CMH method in addition to conditional logistic regression, as Vines and Farrington reported that the estimation of the CMH method was approximately unbiased.\(^{(22)}\) Actually, the present study showed that the estimated value of the CMH method was lower than that of conditional logistic regression, especially for antiepileptic agents (1.74 vs. 2.45, respectively). The present study showed that the crude and adjusted ORs calculated from conditional logistic regression were similar, and thus, crude ORs from CMH methods would be presum-
ably right as estimated values. Therefore, the OR for antiepileptic agents is thought to be approximately 2.0, not 2.5, as described at the start of this discussion.

There are also some limitations based on claims data, i.e., information bias such as inaccuracy of disease and medication use, which has been described in detail elsewhere. It is difficult to carry out validation studies to confirm accuracy in Japan, where links between social security numbers and databases are not established. For this reason, we did not conduct validation studies, but we carefully identified fragility fractures by connecting diagnostic codes with modifier codes in addition to diagnostic codes, diagnosis date, and radiographic examination, as described in Materials and Methods.

Regardless of the limitations, the results of the present study suggest that antiepileptic agents have the highest risk of fragility fracture among a wide range of CNS agent classes in elderly non-opioid users in Japan. Elderly individuals who use antiepileptic agents or combinations of antiepileptic agents and the CNS agent classes with the next-highest ORs, such as anti-dementia agents and antipsychotics, should be carefully monitored.

Acknowledgments We thank the Ministry of Health, Labour and Welfare for generating and making the dataset from the NDB Japan available for our study. This work was supported by JSPS KAKENHI Grant Number JP15K08121.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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