**Supplemental materials**

**Subgroup analysis**

Subgroup analyses were performed to assess the effects of sex, age, and clinical departments on the following endpoints.

**Numbers/proportions of patients prescribed**

The proportion of patients prescribed loxoprofen was higher for the group 15 to 64 years (40.0% of all patients prescribed the drugs for continued prescriptions) than for those aged ≤ 14 years (10.8%) and ≥ 65 years (22.9%). Acetaminophen was prescribed more commonly to pediatric patients aged ≤ 14 years (27.5%) than to patients in the other age groups (≤ 11.7%). The proportion of patients prescribed drugs for continued prescriptions was different for each age group. Regarding clinical departments, pregabalin was more commonly prescribed in the anesthesiology/pain clinic (patient proportion: 29.0%) and neurology (18.2%) than in other clinical departments (1.1% to 13.6%). Regarding pro re nata (PRN) prescriptions, the proportion of patients prescribed loxoprofen was high in orthopedic surgery, general surgery, neurosurgery, neurology, and dentistry, whereas the proportion prescribed acetaminophen was high in general internal medicine, anesthesiology/pain clinic, dermatology, diabetes medicine, and pediatrics. The commonly used continued and PRN prescriptions were different for each clinical department.

**Median daily prescription doses**

For pregabalin and tramadol & acetaminophen (TA) combination, the median daily prescription doses were higher for males than for females (pregabalin: male 100 mg, female 75 mg, and Tramadol & acetaminophen combination: 112.5 mg and 75 mg, respectively). Pregabalin, Shakuyaku-kanzo-to, and tramadol & acetaminophen combination were prescribed at higher doses for patients aged 15 to 64 years than for patients aged ≥ 65 years (pregabalin: 15 to 64 years: 100 mg and ≥ 65 years: 75 mg; Shakuyaku-kanzo-to: 6,000 mg and 4,000 mg; and tramadol & acetaminophen combination: 113 mg and 75 mg, respectively) (Table S2). By clinical departments, the daily prescription dose of acetaminophen was higher in anesthesiology/pain clinics than in other clinical departments (1,800 mg and 600 to 1,500 mg, respectively).

**Co-prescription patterns**

The proportion of patients prescribed one drug was higher for the pediatric patient group (≤ 14 years) than for those aged 15 to 64 years and ≥ 65 years. In patients aged 15 to 64 years and ≥ 65 years, the commonly used combinations of 2 drugs were pregabalin + loxoprofen and pregabalin + celecoxib (15 to 64 years: 1.4% and 0.9%, respectively; ≥ 65 years: 0.8% and 1.2%, respectively). By clinical departments, the proportions of patients prescribed one drug were higher in pediatrics and dentistry (95.1% and 97.8%, respectively) than in the other clinical departments. In contrast, the percentages of patients receiving combination prescriptions were higher in anesthesiology/pain clinics (29.4%) than in the other departments. Pregabalin + loxoprofen was the most common combination prescription in orthopedic surgery (1.9%), general surgery (0.9%), and neurology (0.4%). Pregabalin + celecoxib was commonly prescribed in orthopedic surgery (1.8%), anesthesiology/pain clinic (0.8%), general surgery (0.4%), neurosurgery (0.4%), and neurology (0.3%).

**Distribution of initial doses and changes from the initial doses**

Pregabalin was prescribed at higher doses (median) in male patients (100 mg and 150 mg) than in female patients (75 mg and 100 mg) within 14 days to 90 days; these doses in male and female patients were still lower than the approved dose. Increases to higher doses of pregabalin (100 mg and 150 mg) and acetaminophen combinations (500 mg and 600 mg) were observed more frequently in patients aged 15 to 64 years than in patients of other age groups. Most notably, patients aged ≥ 65 years who were prescribed acetaminophen showed a tendency to not have increased doses. With respect to clinical departments, acetaminophen was prescribed at a higher dose (1,800 mg) in anesthesia/pain clinics than in the other clinical departments (600 to 1,500 mg).

We investigated the initial doses of pregabalin and duloxetine in the highest proportion of patients treated with prescribed doses (> 150 to ≤ 300 mg and [40 or 60 mg], respectively), which included approved doses. In the analysis of the initial pregabalin dose, the proportion of patients was the highest for those prescribed > 25 to ≤ 50 mg (32.5%), followed by > 100 to ≤ 150 mg (22.5%) and > 50 to ≤ 75 mg (15.8%). The dosage in patients who were initially prescribed > 25 to ≤ 50 mg and > 50 to ≤ 75 mg increased up to 90 days (39.5% and 32.9%, respectively), whereas low dosage increases were observed in patients initially prescribed > 100 to ≤ 150 mg (14.4%). Low proportions (0.9% to 8.1%) of patients who maintained or achieved a prescribed dose of > 150 to ≤ 300 mg, including the approved dose (300 mg), were observed among those prescribed initial doses of < 25 mg and > 100 to ≤ 150 mg. In contrast, initial doses of > 150 to ≤ 300 mg pregabalin had been prescribed to the highest proportion (approximately 85%) of patients who maintained or achieved a prescribed dose of > 150 to ≤ 300 mg.

Regarding duloxetine, patients who were prescribed ≤ 20 mg as an initial dose accounted for the majority (76.7%). The proportion of patients whose initial dose was ≤ 20 mg and who showed a dosage increase up to 90 days accounted for 45.4%, whereas the doses of patients who were initially prescribed > 20 to ≤ 40 mg or > 40 to ≤ 60 mg were increased minimally up to 90 days (7.4% and 0%, respectively). Initial doses of > 40 to ≤ 60 mg duloxetine had been prescribed to the highest proportion (approximately 80%) of patients who maintained or achieved a prescribed dose of > 40 to ≤ 60 mg, including the approved dose (40 or 60 mg).

**Duration of continued prescription and medication possession ratio (MPR)**

The proportion of patients aged ≥ 65 years who reached the continued prescription period of > 90 days was the highest with duloxetine (36.6%), followed by pregabalin (34.3%) and neurotropin (32.9%). Regarding clinical departments, in anesthesiology/pain clinics, the proportions of patients receiving continued prescriptions for > 90 days were high for acetaminophen (27.2% and 13.3% for the entire clinical department group), neurotropin (35.7% and 26.3%, respectively), and pregabalin (38.3% and 29.2%, respectively). In neurology, the proportions of patients prescribed celecoxib (34.0% and 13.6% for the entire clinical department group), Shakuyaku-kanzo-to (35.2% and 16.6%, respectively) and tramadol & acetaminophen combination (41.7% and 26.2%, respectively) for > 90 days were increased.

**Treatment-discontinuation rate**

The CTD rates for pregabalin, neurotropin, and tramadol & acetaminophen combination in patients aged ≥ 65 years did not exceed 70% within 90 days, but only duloxetine did not reach 70% within 90 days in all age groups. By clinical departments, in anesthesiology/pain clinics and neurology, there was a tendency for the CTD rates to exceed 70% for a longer period. Most notably, the CTD rates in neurology did not exceed 70% within 90 days for celecoxib, pregabalin, Shakuyaku-kanzo-to, neurotropin, tramadol & acetaminophen combination, and duloxetine.

**Table S1.** Number of patients prescribed drugs during the continued prescription and PRN prescription periods, including ≤ 7 days after the first prescription date.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Total number of patients (%)** | | **Continued prescription** | | | | **PRN**  **Prescription** | |
| **Number of patients (%)** | | **Number of patients × days** | **Mean prescription days** | **Number of patients (%)** | |
|  | 2,042,302 |  | 1,306,819 |  |  |  | 864, 864 |  |
| Acetaminophen | 753,426 | (36.9) | 215,461 | (16.5) | 2, 135,215 | 9.9 | 545,531 | (63.1) |
| Loxoprofen | 645,590 | (31.6) | 413,924 | (31.7) | 5, 363,493 | 13.0 | 239,009 | (27.6) |
| Acetaminophen combinations | 228,858 | (11.2) | 222,952 | (17.1) | 1,315,843 | 5.9 | 6,543 | (0.8) |
| Celecoxib | 114,991 | (5.6) | 109,607 | (8.4) | 2, 949,333 | 26.9 | 6,066 | (0.7) |
| Kakkon-toa | 57, 511 | (2.8) | 56,986 | (4.4) | 512,790 | 9.0 | 544 | (0.1) |
| Pregabalin | 54,523 | (2.7) | 54,270 | (4.2) | 2,490,753 | 45.9 | 378 | (0.0) |
| Ibuprofen | 49,987 | (2.4) | 36,598 | (2.8) | 231,194 | 6.3 | 13,618 | (1.6) |
| Diclofenac | 46,543 | (2.3) | 28,494 | (2.2) | 404,916 | 14.2 | 18,336 | (2.1) |
| Codeine | 37,221 | (1.8) | 29,502 | (2.3) | 263,264 | 8.9 | 7,983 | (0.9) |
| Shakuyaku-kanzo-toa | 28,228 | (1.4) | 21,754 | (1.7) | 713,410 | 32.8 | 6,616 | (0.8) |
| Neurotropin | 21,317 | (1.0) | 21,257 | (1.6) | 798,986 | 37.6 | 75 | (0.0) |
| Tiaramide | 17,086 | (0.8) | 16,591 | (1.3) | 98,183 | 5.9 | 502 | (0.1) |
| TA combination | 16,112 | (0.8) | 15,133 | (1.2) | 620,140 | 41.0 | 1,162 | (0.1) |
| Mefenamic acid | 14,578 | (0.7) | 10,327 | (0.8) | 64,013 | 6.2 | 4,276 | (0.5) |
| Lornoxicam | 14,929 | (0.7) | 11,304 | (0.9) | 172,212 | 15.2 | 3,669 | (0.4) |
| Etodolac | 13,571 | (0.7) | 12,828 | (1.0) | 270,371 | 21.1 | 791 | (0.1) |
| Mao-bushi-saishin-toa | 13,270 | (0.6) | 13,198 | (1.0) | 97,497 | 7.4 | 76 | (0.0) |
| Duloxetine | 13,229 | (0.6) | 13,215 | (1.0) | 700,179 | 53.0 | 21 | (0.0) |
| Diazepam | 9,751 | (0.5) | 6,793 | (0.5) | 268,487 | 39.5 | 3, 163 | (0.4) |
| Cilostazol | 9,571 | (0.5) | 9,571 | (0.7) | 732,272 | 76.5 | 0 | (0.0) |

a Traditional Japanese herbal medicines.

PRN: pro re nata (as needed); TA combination: tramadol & acetaminophen combination.

**Table S2.** Effects of age on median daily prescription doses for continued prescriptions (subgroup analysis).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **≤ 14 years** | | | |  | **15 to 64 years** | | | |  | ***≥* 65 years** | | | | |
| **Number of patients** |  | **Total dose (mg)** | **Median daily prescription dose (mg)** |  | **Number of patients** |  | **Total dose (mg)** | **Median daily prescription dose (mg)** |  | **Number of patients** |  | **Total dose (mg)** | **Median daily prescription dose (mg)** | |
| Loxoprofen | 748 | Q1 | 1,680 | 120 |  | 106,460 | Q1 | 2,460 | 180 |  | 48,566 | Q1 | 2,520 | 180 |
|  |  | Median | 2,520 | 180 |  |  | Median | 2,520 | 180 |  |  | Median | 2,520 | 180 |
|  |  | Q3 | 2,520 | 180 |  |  | Q3 | 5,040 | 180 |  |  | Q3 | 5,400 | 180 |
| Celecoxib | 262 | Q1 | 2,800 | 200 |  | 35,204 | Q1 | 2,800 | 200 |  | 44,191 | Q1 | 2,800 | 200 |
|  |  | Median | 2,800 | 200 |  |  | Median | 4,000 | 200 |  |  | Median | 5,600 | 200 |
|  |  | Q3 | 3,550 | 200 |  |  | Q3 | 6,800 | 200 |  |  | Q3 | 11,200 | 200 |
| Acetaminophen | 1,912 | Q1 | 5,200 | 500 |  | 19,916 | Q1 | 9,600 | 900 |  | 24,902 | Q1 | 12,600 | 800 |
|  |  | Median | 8,400 | 600 |  |  | Median | 16,800 | 1,200 |  |  | Median | 22,500 | 1,200 |
|  |  | Q3 | 12,600 | 900 |  |  | Q3 | 27,000 | 1,500 |  |  | Q3 | 50,400 | 1,500 |
| Pregabalin | 29 | Q1 | 1,250 | 50 |  | 22,409 | Q1 | 1,400 | 50 |  | 24,343 | Q1 | 1,400 | 50 |
|  |  | Median | 2,100 | 50 |  |  | Median | 3,150 | 100 |  |  | Median | 3,500 | 75 |
|  |  | Q3 | 4,500 | 115 |  |  | Q3 | 7,350 | 150 |  |  | Q3 | 7,350 | 137 |
| Acetaminophen combinations | 487 | Q1 | 725 | 75 |  | 12,070 | Q1 | 4,500 | 450 |  | 7,561 | Q1 | 4,500 | 450 |
|  | Median | 2,250 | 225 |  |  | Median | 5,250 | 450 |  |  | Median | 4,950 | 450 |
|  | Q3 | 4,200 | 400 |  |  | Q3 | 6,750 | 500 |  |  | Q3 | 6,300 | 450 |
| Shakuyaku-kanzo-to | 47 | Q1 | 35,000 | 2,500 |  | 5,430 | Q1 | 70,000 | 2,500 |  | 12,084 | Q1 | 70,000 | 2,500 |
|  | Median | 70,000 | 3,000 |  |  | Median | 105,000 | 6,000 |  |  | Median | 105,000 | 4,000 |
|  | Q3 | 105,000 | 6,750 |  |  | Q3 | 225,000 | 7,500 |  |  | Q3 | 225,000 | 7,500 |
| Neurotropin | 34 | Q1 | 224 | 16 |  | 8,180 | Q1 | 224 | 16 |  | 8,825 | Q1 | 224 | 16 |
|  |  | Median | 294 | 16 |  |  | Median | 368 | 16 |  |  | Median | 504 | 16 |
|  |  | Q3 | 610 | 16 |  |  | Q3 | 784 | 16 |  |  | Q3 | 1,184 | 16 |
| TA combination | 5 | Q1 | 1,050 | 75 |  | 6,287 | Q1 | 1,575 | 75 |  | 6,414 | Q1 | 1,575 | 75 |
|  | Median | 2,100 | 75 |  |  | Median | 3,150 | 113 |  |  | Median | 3,375 | 75 |
|  | Q3 | 2,100 | 100 |  |  | Q3 | 6,300 | 150 |  |  | Q3 | 6,825 | 113 |
| Diclofenac | 43 | Q1 | 538 | 50 |  | 8,521 | Q1 | 1,050 | 75 |  | 2,791 | Q1 | 1,050 | 75 |
|  |  | Median | 700 | 50 |  |  | Median | 1,050 | 75 |  |  | Median | 1,400 | 75 |
|  |  | Q3 | 1,050 | 75 |  |  | Q3 | 2,100 | 75 |  |  | Q3 | 2,625 | 75 |
| Duloxetine | 23 | Q1 | 650 | 20 |  | 7,258 | Q1 | 560 | 20 |  | 4,601 | Q1 | 560 | 20 |
|  |  | Median | 1,800 | 20 |  |  | Median | 1,200 | 20 |  |  | Median | 1,260 | 20 |
|  |  | Q3 | 3,220 | 33 |  |  | Q3 | 2,800 | 40 |  |  | Q3 | 2,520 | 37 |

TA combination: tramadol & acetaminophen combination; Q1: first quartile; Q3: third quartile.

**Gap period**

**Gap period of continued prescription (deemed period of continued prescription)**

The continued prescription period was defined as the period of continued prescription, and the data obtained were used for the results in this article. The gap periods of continued prescription were the periods involving the lowest prescribed doses which were reduced at the patient's own discretion. Gap periods of continued prescriptions were not collected as endpoints but were used for evaluating the continued prescription periods.

The minimum specification amount was defined as follows:

When the dosage form was a tablet, “the minimum specification amount” was defined as the content of active ingredients in one tablet. When the dosage forms were dry syrup, fine granules, powders, granules, or other measured forms, “the minimum specification amount” was defined as only one of the doses/day described in the package insert.

In this study, the gap period of continued prescription was defined as the period during which the prescription was deemed to be continuous and was defined as the longest number of days to completion of treatment after taking “the minimum specification amount” of drugs every day plus 3 days. The boundary values for +3 days were as indicated in the following example: if the final prescription date based on the “minimum specification amount” was April 1, it was judged a continued prescription if the prescription was renewed by April 4. After the first prescription, if the prescription-to-prescription interval fell within the gap period of continued prescription, the prescription was deemed to be continuous. All other cases were deemed to be treatment discontinuation.

When different dosage forms of the same drug were prescribed on the same day, the number of prescription days was calculated based on the sum of the prescription doses of the “minimum specification amount” in calculating the gap period of continued prescription.

An example of calculation for the gap period is shown in Figure S1.

**Figure S1.** An example of calculation for the gap period.

**Assessment of continued prescription during the additional follow-up period**

The continued prescription in patients during the additional follow-up period was assessed only when the prescription interval between the final prescription date and March 31, 2018 was more than or equal to the gap period of continued prescription. However, even when the interval was less than the gap period of continued prescription, continuation assessment was performed if the prescription could be confirmed.

The assessed cases of continued prescription during the additional follow-up period are shown in Figure S2.



**Figure S2.** Assessed cases of continued prescription during the additional follow-up period.