

# Comparison of the Effectiveness of Pharmacological Treatments for Patients with Chronic Low Back Pain: A Nationwide, Multicenter Study in Japan

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## Abstract:

**Introduction:** Chronic low back pain (CLBP) is a leading cause of disability, yet there is limited high-quality evidence to identify the most suitable pharmacological therapy. The purpose of this Japanese nationwide, multicenter, prospective study was to compare the effectiveness of four representative drug therapies—acetaminophen, celecoxib, loxoprofen, and a tramadol and acetaminophen (T+A) combination drug—to establish evidence for a drug of choice for CLBP.

**Methods:** Patients with CLBP (N=471) received one of the four treatments and were evaluated, prospectively and comprehensively, once every month for six months using a visual analog scale (VAS) for LBP, the Japanese Orthopedic Association (JOA) score, the JOA Back Pain Evaluation Questionnaire (JOABPEQ), the Roland-Morris Disability Questionnaire (RDQ), the EuroQol five-dimensions three-levels (EQ-5D-3L), and the Short Form-8 item health survey (SF-8). We conducted multivariable linear regression analyses of the four drugs at 1 and 6 months after drug allocation. Differences with  $P < 0.05$  were considered statistically significant.

**Results:** Patients who received acetaminophen showed a significant improvement from baseline in the mental health subscale of the JOABPEQ at one month ( $P=0.02$ ) and the JOA score at six months ( $P<0.01$ ). None of the other outcome measures among the four drugs differed significantly. Across groups, all outcome measures, except the mental component summary (MCS) score of the SF-8, improved equivalently, although most measurements showed no obvious cumulative effect over six months. The MCS score of the SF-8 decreased gradually over six months in all groups.

**Conclusions:** Most of the outcome measures among the treated groups were not significantly different, indicating similar treatment effects of the four drugs for CLBP. Our study indicated the limit of each outcome measure for evaluating the patient status, suggesting that a single outcome measure is insufficient to reflect treatment effectiveness.

**Keywords:**

chronic low back pain, pharmacological treatment, analgesics, effectiveness

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## Introduction

Chronic low back pain (CLBP) is a leading cause of disability in many countries and a prevalent disorder imposing a substantial economic burden worldwide<sup>1</sup>. Patients with CLBP are high consumers of healthcare resources due to clinic and/or hospital visits and the use of prescription medications<sup>2</sup>. The results of the Japanese National Livelihood Survey, conducted in 2016, showed that LBP was the most widely reported subjective symptom of a disorder or disease in men and the second-most widely reported symptom in women. It was the most common musculoskeletal disorder leading to hospital or clinic attendance<sup>3</sup>. Also, a recent Japanese survey of 11,507 individuals found that the prevalence of chronic musculoskeletal pain, using a visual analog scale (VAS) score of  $\geq 50$  mm, was 15.4%. Among the subpopulation with chronic musculoskeletal pain, the most commonly reported pain site was the lower back (65%). The lower back was also the most frequently reported site of pain that persisted for  $\geq 6$  months<sup>4</sup>. In Japan, from an economic standpoint, the mean annual direct and indirect per-patient costs expended on CLBP are reported to be ¥1,820,297 (\$15,239 or €12,551) and ¥1,479,899 (\$12,389 or €10,203), respectively, and most of the direct costs are related to hospital expenses<sup>5</sup>. To reduce medical and associated costs, in 2010, the Japanese Ministry of Health, Labour, and Welfare announced a proposal for a countermeasure against chronic pain, one designed to promote research to establish effective treatments for patients burdened with it. Despite this effort, and several treatment guidelines on managing CLBP<sup>6-9</sup>, only 36% of patients reported satisfaction with their treatment<sup>4</sup>. Based on these findings, the Project Committee of the Japanese Society for Spine Surgery and Related Research (JSSR) conducted a nationwide, prospective, clinical, and economic study of pharmacological treatments for CLBP to evaluate four leading drugs: acetaminophen (Calonal), celecoxib (Celecox, a cyclooxygenase-2 [Cox2] inhibitor), loxoprofen sodium (Loxonin, a nonsteroidal anti-inflammatory drug), and a tramadol (a weak opioid) and acetaminophen (T+A) combination drug (Tramacet). A recent report indicated that the pharmacological management of CLBP over six months

was cost effective when evaluated by quality-adjusted life years calculated using the EuroQol five-dimensions three-level (EQ-5D-3L) instrument<sup>10</sup>. However, although pharmacological treatment is a recognized initial step in treating CLBP, there is limited high-quality evidence of which pharmacological therapy is best for treating CLBP effectively and efficiently<sup>11</sup>. Therefore, in this study, we compared the effectiveness of acetaminophen, celecoxib, loxoprofen, and the T+A combination drug, the four drugs available for treating CLBP. We used several outcome measures to establish evidence of the optimal pharmacological treatment option for CLBP.

## Materials and Methods

### Study patients

This study was performed following the Declaration of Helsinki and ethical guidelines for medical and health research involving human subjects indicated by the Ministry of Health, Labour, and Welfare, Japan. The Institutional Review Board of the authors' affiliated institutions approved this study. Patients were recruited by 28 university institutions and their associated hospitals from January 2014 to June 2016. Inclusion and exclusion criteria have been described previously<sup>10</sup>. Briefly, eligible patients met the following criteria: (1) main complaint of CLBP for  $\geq 3$  months, (2) aged 20 to 85 years, and (3) Brief Scale for Psychiatric Problems in Orthopedic Patients (BS-POP) score  $<10$  on the physician version and  $<15$  on the patient version<sup>12</sup>. Exclusion criteria were as follows: (1) prescription of two or more drugs from among acetaminophen, celecoxib, loxoprofen sodium, and/or the T+A combination drug during the research period, (2) coexistence of a gastrointestinal disorder with hemorrhage, (3) concomitant severe cardiac, hepatic, or renal disease, (4) hematologic disease, as with bleeding diathesis, (5) dementia or another psychiatric disorder for which an appropriate LBP evaluation is difficult, (6) coexistent or previous history of alcohol or drug dependence, and (7) history of a malignant neoplasm within five years. The BS-POP score was obtained to exclude patients with certain

**Table 1.** Study Protocol.

Time point		Enrolment	Allocation	1 month	2 months	3 months	4 months	5 months	6 months
Eligibility screening		X							
Interview for patient background		X							
Informed consent		X							
Interventions	Medical examination	X		X	X	X	X	X	X
	Prescription of target drugs		X	X	X	X	X	X	(X)
Assessments	EQ-5D-3L, RDQ		X (Baseline)	X	X	X	X	X	X
	JOABPEQ, VAS, SF-8								

psychological factors affecting CLBP. JSSR member physicians obtained informed consent from all individual patients who agreed to participate in this research and ensured confidentiality of information.

Patients were prescribed one of the four drugs of interest for treating CLBP based on the treating physician's choice. Drug assignment was not randomized or specified via a protocol.

#### Data collection

Table 1 shows the study protocol. At the time of enrollment, we recorded baseline characteristics, including age, sex, body mass index (BMI), CLBP duration and comorbidities (osteoporosis, hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, renal dysfunction, liver dysfunction, respiratory disease, endocrine disease, autoimmune disease [rheumatoid arthritis, etc.], and psychiatric disorders, including depression) for which treatment is necessary. We also documented patients' histories of malignant tumors, smoking habits, employment status, exercise frequency, number of live-in family members, and personal hobbies. We obtained plain X-ray images of the lumbar spine and evaluated spondylotic changes, including the Cobb angle and existing vertebral fractures. The Center for Epidemiologic Studies Depression Scale (CES-D) score and the BS-POP score were also collected at study entry. Blood samples were obtained at study entry and at the three-month follow-up to evaluate existing and induced side effects to assess whether patients could continue the prescribed treatment for another three months.

During the six-month follow-up period, patients visited the outpatient clinic once every month. No other prescription medication (e.g., pregabalin, muscle relaxants, serotonin, and/or norepinephrine reuptake inhibitors), except the four drugs being evaluated, was allowed pain control during the six-month follow-up period.

#### Clinical outcome measures

To evaluate each drug's effectiveness, we obtained patients' scores for pain intensity using the VAS for LBP. Specific lumbar disease measures were acquired using the Japanese Orthopedic Association (JOA) score, JOA Back Pain Evaluation Questionnaire (JOABPEQ), and the Roland-

Morris Disability Questionnaire (RDQ), as well as outcome measures of health-related quality of life using the EQ-5D-3L and the Short Form-8 (SF-8). These scores were evaluated at the time of drug allocation as a baseline and monthly during the 6-month follow-up (Table 1). The JSSR Project Committee prepared the datasheet, including the information above, and the physician returned the sheet to our office with the necessary information three and six months after allocation.

The changes from baseline in the VAS score for LBP, JOA score, JOABPEQ score, RDQ score, EQ-5D score, physical component summary (PCS) score, and the mental component summary (MCS) score of the SF-8 were compared between the four drugs at six time points during the follow-up, from 1 to 6 months post-baseline.

#### Statistical analysis

Demographic and disease characteristics of patients at baseline were summarized using medians and interquartile ranges (25% and 75% percentile values) for continuous variables and numbers and percentages for categorical variables (Table 2). Variables were compared among treatment groups using baseline data and Kruskal-Wallis and chi-square tests for continuous and categorical variables, respectively.

We conducted multivariable linear regression analyses to compare these treatments' effects on the change in each outcome measure over six months. The analysis included the change from baseline for each outcome at each time point as a dependent variable. Independent variables indicated that the medicine was prescribed continuously from baseline, observation, and cross-product terms. These models were adjusted for baseline covariates of age, sex, BMI, smoking status, disease duration, history of cancer, osteoporosis, spine surgery, spine disease, medicine (nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, acetaminophen, a T+A combination drug, neuropathic pain remedies, antidepressants, and opioids), Center for Epidemiologic Studies Depression Scale (CES-D), exercise status, work, hobbies, number of family members, and number of comorbidities. The dataset contained values for repeated measurements of a single patient until the baseline medicine had been discontinued or another medicine had been prescribed in addition to the baseline medicine. The repeated measurements were

**Table 2.** Patient Characteristics.

	Acetaminophen	Celecoxib	Loxoprofen	T+A combination drug	P-value	Missing (%)
n	94	170	89	118		
Age, median (IQR), years	73.0 (67.0, 77.0)	75.0 (68.3, 78.8)	72.0 (62.0, 77.0)	72.0 (64.0, 77.0)	<b>0.012</b>	2.3
Sex, n (%)	male	37 (39.4)	65 (38.9)	38 (43.2)	0.491	0.8
	female	57 (60.6)	102 (61.1)	50 (56.8)		
BMI, median (IQR), kg/m <sup>2</sup>	23.7 (21.4, 25.9)	24.1 (21.8, 26.5)	23.4 (21.1, 25.8)	23.6 (20.9, 26.4)	0.522	5.1
Duration of CLBP, median (IQR), days	1050.0 (360.0, 2007.5)	730.0 (365.0, 2098.8)	730.0 (390.0, 1825.0)	730.0 (330.0, 2555.0)	0.982	6.4
Osteoporosis, n (%)	-	81.9 (77)	76.5 (130)	78.7 (70)	0.522	0.0
	+	18.1 (17)	23.5 (40)	21.3 (19)		
Hypertension, n (%)	-	76.6 (72)	60.6 (103)	69.7 (62)	<b>0.04</b>	0.0
	+	23.4 (22)	39.4 (67)	30.3 (27)		
Diabetes mellitus, n (%)	-	89.4 (84)	82.9 (141)	92.1 (82)	0.169	0.0
	+	10.6 (10)	17.1 (29)	7.9 (7)		
Coronary artery disease, n (%)	-	92.6 (87)	92.9 (158)	95.5 (85)	0.812	0.0
	+	7.4 (7)	7.1 (12)	4.5 (4)		
Cerebrovascular disease, n (%)	-	94.7 (89)	98.2 (167)	98.9 (88)	0.263	0.0
	+	5.3 (5)	1.8 (3)	1.1 (1)		
Renal dysfunction, n (%)	-	92.6 (87)	96.5 (164)	97.8 (87)	0.326	0.0
	+	7.4 (7)	3.5 (6)	2.2 (2)		
Liver dysfunction, n (%)	-	97.9 (92)	97.1 (165)	100.0 (89)	0.392	0.0
	+	2.1 (2)	2.9 (5)	0.0 (0)		
Respiratory disease, n (%)	-	96.8 (91)	98.2 (167)	97.8 (87)	0.866	0.0
	+	3.2 (3)	1.8 (3)	2.2 (2)		
Endocrine disease, n (%)	-	94.7 (89)	97.1 (165)	95.5 (85)	0.261	0.0
	+	5.3 (5)	2.9 (5)	4.5 (4)		
Rheumatoid arthritis, n (%)	-	100.0 (94)	97.1 (165)	98.9 (88)	0.342	0.0
	+	0.0 (0)	2.9 (5)	1.1 (1)		
Other autoimmune diseases, n (%)	-	98.9 (93)	99.4 (169)	97.8 (87)	0.658	0.0
	+	1.1 (1)	0.6 (1)	2.2 (2)		
Depression, n (%)	-	98.9 (93)	99.4 (169)	100.0 (89)	0.818	0.0
	+	1.1 (1)	0.6 (1)	0.0 (0)		
Other psychiatric disorders, n (%)	-	98.9 (93)	98.8 (168)	98.9 (88)	0.715	0.0
	+	1.1 (1)	1.2 (2)	1.1 (1)		
Past history of malignant tumor, n (%)	-	93.6 (88)	92.4 (157)	93.3 (83)	0.861	0.0
	+	6.4 (6)	7.6 (13)	6.7 (6)		
Current smoking habit, n (%)	-	90.4 (85)	90.0 (153)	93.3 (83)	0.851	0.0
	+	9.6 (9)	10.0 (17)	6.7 (6)		
BS-POP for patients, median (IQR)	12.0 (11.0, 14.0)	12.0 (11.0, 14.0)	13.0 (11.0, 14.0)	13.0 (11.0, 15.0)	<b>0.028</b>	7.2
BS-POP for medical personnel, median (IQR)	8.0 (8.0, 9.0)	8.0 (8.0, 9.0)	8.5 (8.0, 9.0)	9.0 (8.0, 9.0)	<b>0.038</b>	4.5
CES-D, median (IQR)	14.0 (9.0, 22.0)	14.0 (11.0, 20.0)	14.0 (9.0, 22.3)	15.0 (10.8, 20.0)	0.98	3.8
EQ-5D-3L, median (IQR)	0.65 (0.59, 0.77)	0.65 (0.57, 0.77)	0.65 (0.57, 0.72)	0.65 (0.55, 0.69)	0.475	3.4
Total JOA score, median (IQR)	19 (16, 22)	20 (17, 23)	20 (17, 22)	18 (15, 21)	<b>0.008</b>	3.8
RDQ score, median (IQR)	9 (5, 14)	10 (7, 15)	10 (6, 13)	10 (7, 14)	0.493	2.8
JOABPEQ-low back pain, median (IQR)	43.0 (21.5, 71.0)	43.0 (14.0, 71.0)	43.0 (25.3, 71.0)	43.0 (14.0, 71.0)	0.115	10.6

**Table 2.** Patient Characteristics (continued).

	Acetaminophen	Celecoxib	Loxoprofen	T+A combination drug	P-value	Missing (%)
JOABPEQ-lumbar function, median (IQR)	33.0 (33.0, 66.7)	33.0 (33.0, 58.3)	33.3 (33.0, 58.3)	33.0 (33.0, 58.3)	0.678	8.9
JOABPEQ-walking ability, median (IQR)	43.0 (23.0, 86.0)	43.0 (29.0, 71.0)	50.0 (29.0, 64.0)	43.0 (27.0, 64.0)	0.79	11.3
JOABPEQ-social life function, median (IQR)	51.0 (36.0, 71.0)	51.0 (35.0, 65.0)	51.0 (31.0, 64.0)	50.5 (30.0, 57.5)	0.223	11.3
JOABPEQ-mental health, median (IQR)	51.0 (42.0, 59.8)	50.0 (42.0, 63.0)	53.0 (42.0, 68.0)	50.0 (41.8, 61.3)	0.591	8.5
Visual analogue scale of LBP, median (IQR), mm	50.0 (30.0, 70.0)	55.5 (38.5, 70.3)	57.0 (45.0, 70.0)	55.5 (41.5, 74.3)	0.628	6.6
SF8-PCS score, median (IQR)	37.3 (27.9, 43.3)	38.0 (30.3, 42.0)	37.6 (31.4, 42.7)	35.6 (28.1, 39.9)	0.084	8.1
SF8-MCS score, median (IQR)	48.5 (43.4, 54.6)	49.8 (44.7, 55.0)	49.0 (45.6, 55.3)	49.1 (43.6, 54.7)	0.631	8.1
Spondylotic change in lumbar spine, n (%)	-	25.5 (24)	32.9 (56)	32.6 (29)	0.159	0.0
	+	74.5 (70)	67.1 (114)	67.4 (60)		
	<10°	90.7 (39)	87.8 (72)	91.2 (31)		
Cobb angle of scoliosis, n (%)	≥10° and <30°	7.0 (3)	11.0 (9)	5.9 (2)	0.863	0.0
	≥30°	2.3 (1)	1.2 (1)	2.9 (1)		
	0°	92.7 (97)	88.8 (91)	91.1 (97)		
Vertebral fracture, n (%)	-	93.8 (90)	85.8 (151)	94.4 (84)	0.124	0.0
	+	6.2 (6)	14.2 (25)	5.6 (5)		
	Rarely	55.7 (49)	53.2 (82)	57.8 (48)		
Frequency of exercise, n (%)	Occasionally	9.1 (8)	16.9 (26)	13.3 (11)	0.809	7.0
	Frequently	14.8 (13)	14.9 (23)	12.0 (10)		
	Everyday	20.5 (18)	14.9 (23)	16.9 (14)		
Employment, n (%)	-	25.8 (24)	22.8 (38)	27.0 (24)	0.778	1.5
	+	74.2 (69)	77.2 (129)	73.0 (65)		
Live-in family members, median (IQR), n	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.706	10.8
Hobby, n (%)	-	38.0 (35)	40.5 (66)	42.7 (38)	0.893	3.2
	+	72.0 (57)	59.5 (97)	57.3 (51)		

Abbreviations: T+A, tramadol and acetaminophen

addressed using a Huber-White robust sandwich estimation method, and we estimated robust standard errors. Missing values were imputed using the last observation carried forward method. Statistical hypotheses were tested one and six months after drug allocation, using a two-sided 5% significance level. All statistical inferences were performed using R software version 3.6.0 (<https://cran.r-project.org/>).

## Results

### Baseline demographics

We recruited 471 patients. Table 2 shows patient characteristics at the time of drug allocation. Missing rates for each factor are also listed. The comorbidity of hypertension and age, BS-POP, and total JOA score showed statistically significant differences among the four drug-treatment groups. Loxoprofen and the T+A combination drug were prescribed for patients at a relatively younger age than the other two drugs. There were significant differences in the JOA total score, and the patient and medical personnel version of the BS-POP. However, the maximum differences in

the median value or upper and lower quartiles among the four drugs were within two points. Table 3 shows the mean drug dose and the number of patients in each group. Patient numbers decreased because prescriptions of the four drugs were canceled or changed for unknown reasons. As a result, 230 (48.8%) patients had persisted in the 6-month follow-up after being prescribed one of the four drugs continuously. There were no significant changes in the numbers of patients between the four drugs. The mean doses of each drug prescribed during the six-month follow-up were maintained and were consistent with a standard dose, which had been shown in the previous study using a large-scale prescription database in Japan<sup>13)</sup>.

### Overall 6-month results for each clinical outcome

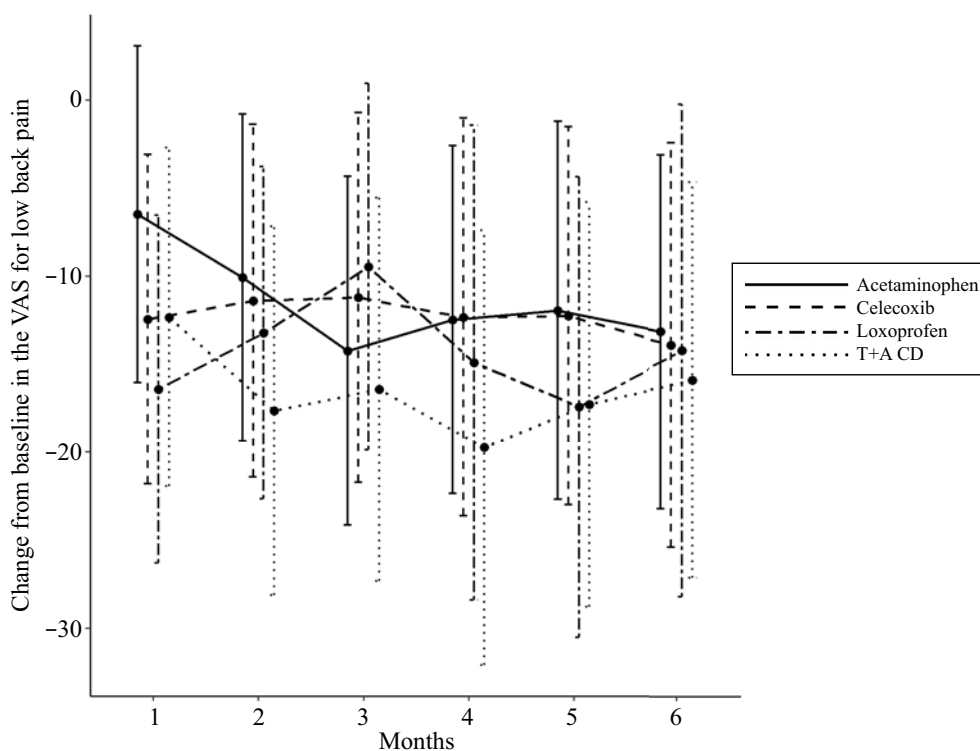
The VAS score for LBP improved from baseline at all time points with a 10-15 mm improvement, showing no obvious cumulative effects over six months (Fig. 1). The JOA score increased in patients taking any of the four drugs over six months. Acetaminophen showed the largest JOA total score improvement at >3 points, indicating a relatively large cumulative effect over six months (Fig. 2). All five subscales



**Table 3.** Mean Drug Dose and Number of Patients.

		Baseline	1 Mo	2 Mo	3 Mo	4 Mo	5 Mo
Acetaminophen	Dose	1112 mg	1121 mg	1095 mg	1167 mg	1170 mg	1157 mg
	n	94	71	57	53	50	47
Celecoxib	Dose	208 mg	211 mg	207 mg	210 mg	210 mg	210 mg
	n	170	136	113	103	95	85
Loxoprofen	Tablets	2.3 T	2.4 T	2.4 T	2.3 T	2.4 T	2.3 T
	n	89	73	59	43	38	34
T+A combination drug*	Tablets	2.7 T	2.8 T	2.9 T	2.9 T	3.0 T	2.9 T
	n	118	95	82	77	70	64

\*One tablet of T+A combination drug includes 37.5 mg of tramadol and 325 mg of acetaminophen.  
Abbreviations: T+A, tramadol and acetaminophen



**Figure 1.** Change from baseline in VAS for low back pain during the follow-up period. Error bars represent 95% confidence intervals.

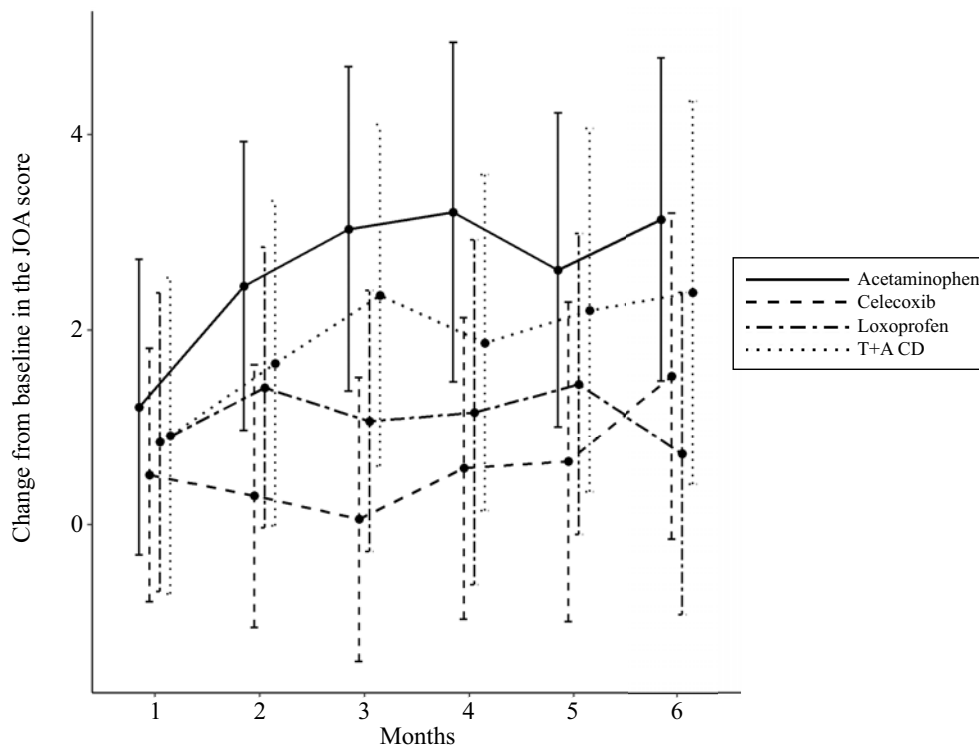
Abbreviations: CD, combination drug; LBP, low back pain; T+A, tramadol and acetaminophen; VAS, visual analog scale

of the JOABPEQ improved with each of the four drugs at all time points, although effectiveness was not cumulative over six months. Among the five subscales, the lumbar function subscale improved most substantially with an effect size >20 points, followed by LBP with a 10-20-point effect size. Finally, walking ability and social life function with a 5-10-point effect size (Fig. 3A-D). The mental health subscale improved the least with an effect size <5 points (Fig. 3E). The RDQ score improved over six months, and a similar tendency for improvement was evident among the four drugs with small cumulative effectiveness noted over six months (Fig. 4). The EQ-5D score increased approximately

0.02 to 0.03 points over one month, and from one to six months, it almost plateaued (Fig. 5). On the SF-8, the PCS score improved across all groups, predominantly by 10 to 20 points at all time points (Fig. 6A). By contrast, the MCS score gradually became worse across all groups during the six-month follow-up period with 0 to 2.5 point effect sizes (Fig. 6B).

**Statistical comparisons 1 and 6 months after drug allocation**

Comparisons were performed one and six months post-baseline. By one month, there was a significant difference



**Figure 2.** Change from baseline for the JOA score during the follow-up period. Error bars represent 95% confidence intervals.

Abbreviations: CD, combination drug; JOA, Japanese Orthopedic Association; T+A, tramadol and acetaminophen

only in the mental health subscale of JOABPEQ ( $P=0.02$ ; Fig. 3E). By contrast, at six months, there was a significant difference only in the JOA score among patients who received one of the four drugs ( $P=0.04$ ; Fig. 2). No statistical difference was noted for other outcome measures.

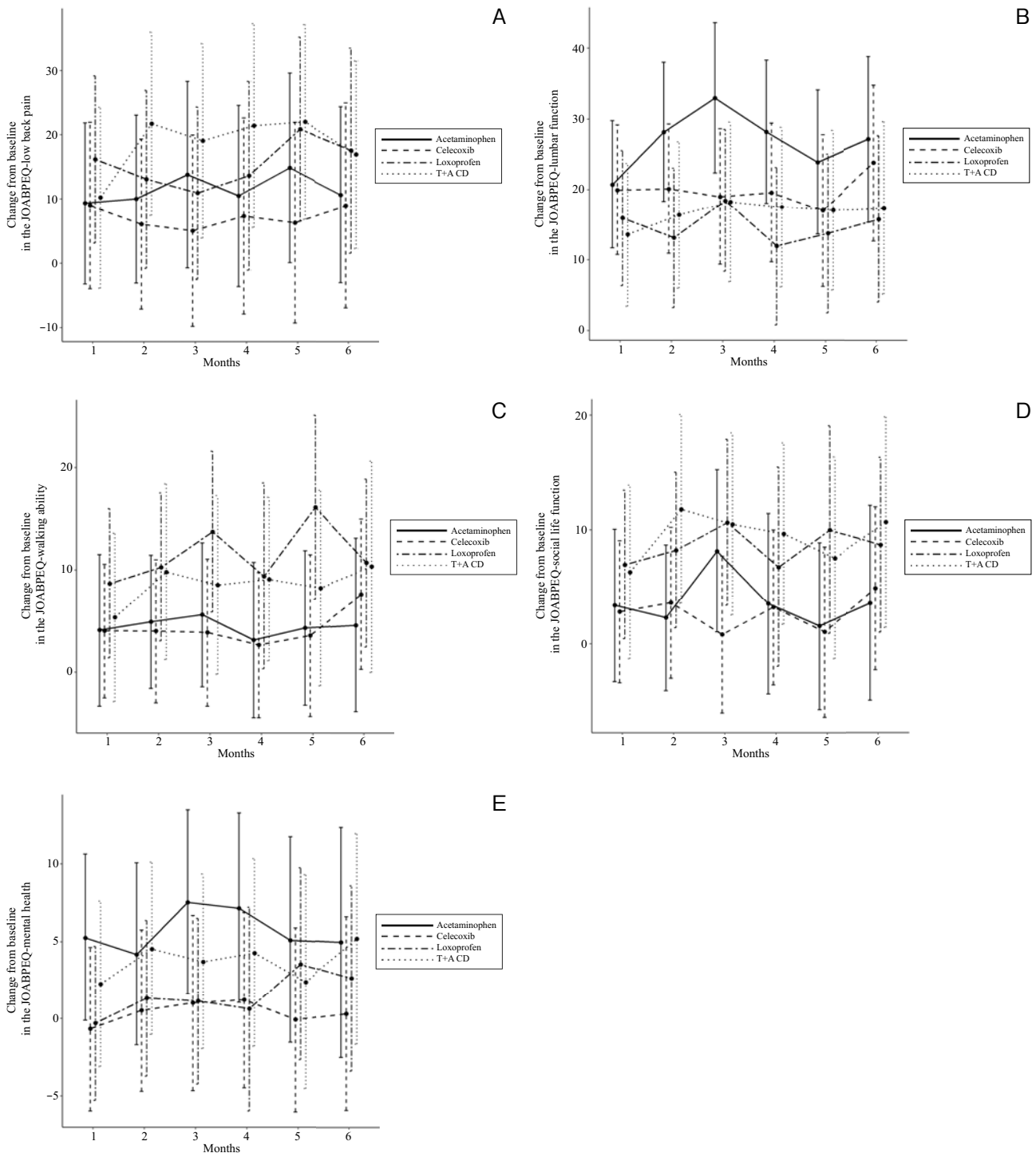
## Discussion

To our knowledge, this is the first report of a Japanese, nationwide, prospective, multicenter study conducted to compare drugs prescribed for CLBP. Recent evidence has shown that pain elimination is not a realistic goal for patients with chronic pain<sup>14</sup>. Furthermore, CLBP is a disease with a complex pathology that includes abnormal conditions of the body and/or mind that can cause discomfort and/or dysfunction<sup>11,15</sup>. For these reasons, a standardized combination of outcome measures was recommended to evaluate pain intensity, functional status, and generic well-being in this study of CLBP.

Based on the outcome measures of 11 randomized clinical trials, Morris et al. evaluated the correlations between RDQ, the PCS of the SF-12, and the Oswestry Disability Index. Using the Pearson correlation coefficient, the correlations were moderately positive, or between 0.4 and 0.6, although crosswalking between scores on different LBP outcome measures is not justifiable<sup>16</sup>. In our current study, a multifaceted evaluation was performed monthly using VAS for LBP, the JOA score, JOABPEQ, RDQ, EQ-5D, and SF-8 instru-

ments, and statistical analyses were conducted on data collected 1 and 6 months after drug allocation.

At the one-month mark, the mental health subscale of the JOABPEQ showed significant differences among the four drugs. Acetaminophen and the T+A combination drug improved by 5 and 2.5 points, respectively; however, by contrast, the scores for loxoprofen and celecoxib worsened. Acetaminophen exerted the largest effect on this subscale throughout six months, followed by the T+A combination drug. Compared with the acetaminophen group, patients in the T+A combination drug group were prescribed a lower amount of acetaminophen at all time points, as indicated in Table 3. Besides the fact that the opioid agonist activity of tramadol conceivably plays a role in improving various mental aspects<sup>17</sup>, there is considerable evidence that the analgesic effect of acetaminophen is at least partly produced via supraspinal activation of descending serotonergic pathways<sup>18</sup>. There is no direct evidence indicating a positive effect on mental health attributable to acetaminophen. However, such an effect may be induced by decreased prostaglandin synthesis in the central nervous system<sup>19</sup>. Although the effects of these two drugs on mental health might be limited because the effect size of the mental health subscale of the JOABPEQ was relatively smaller than the other subscales of the JOABPEQ, and all four drugs had a negative impact on the MCS score of the SF-8 (Fig. 3E, 6 B). LBP is well-characterized by psychological factors<sup>20,21</sup>. In this study, patients with BS-POP scores  $\geq 10$  points for



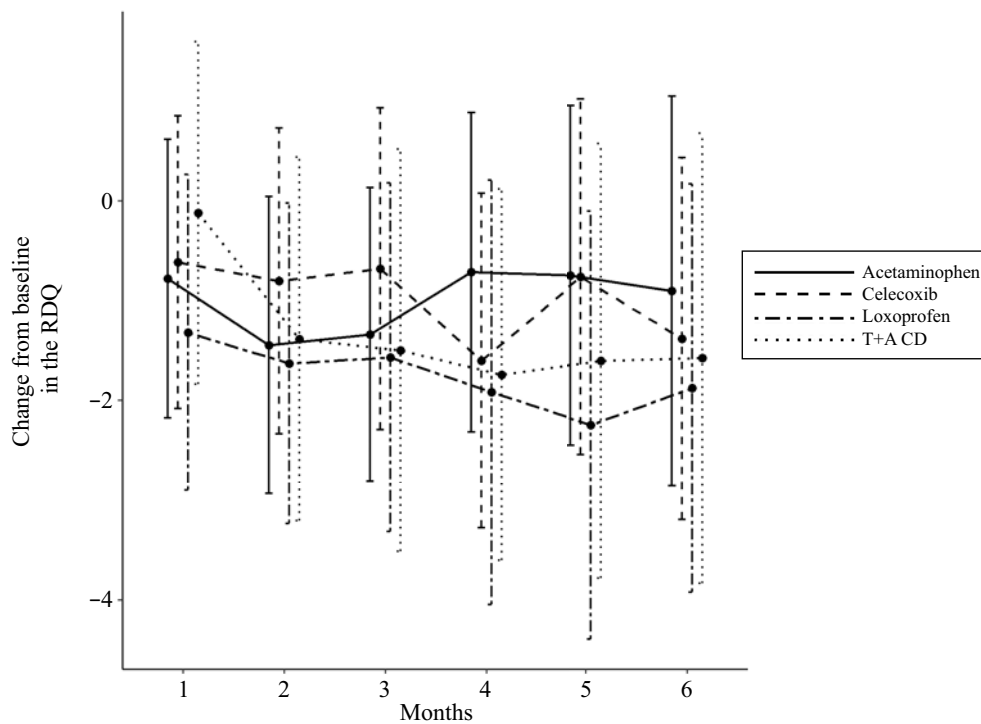
**Figure 3.** Change from baseline in the JOABPEQ score during the follow-up period. Error bars represent 95% confidence intervals. (A) LBP, (B) Lumbar function, (C) Walking ability, (D) Social life function, and (E) Mental health. Abbreviations: CD, combination drug; JOABPEQ, Japanese Orthopedic Association Back Pain Evaluation Questionnaire; T+A, tramadol and acetaminophen

the medical personnel version and  $\geq 15$  points for the patient version, which indicates a substantial proportion of psychiatric problems, were excluded. Even in patients without psychological factors, our results suggest that symptoms related to mental health in patients with LBP do not improve with analgesics alone.

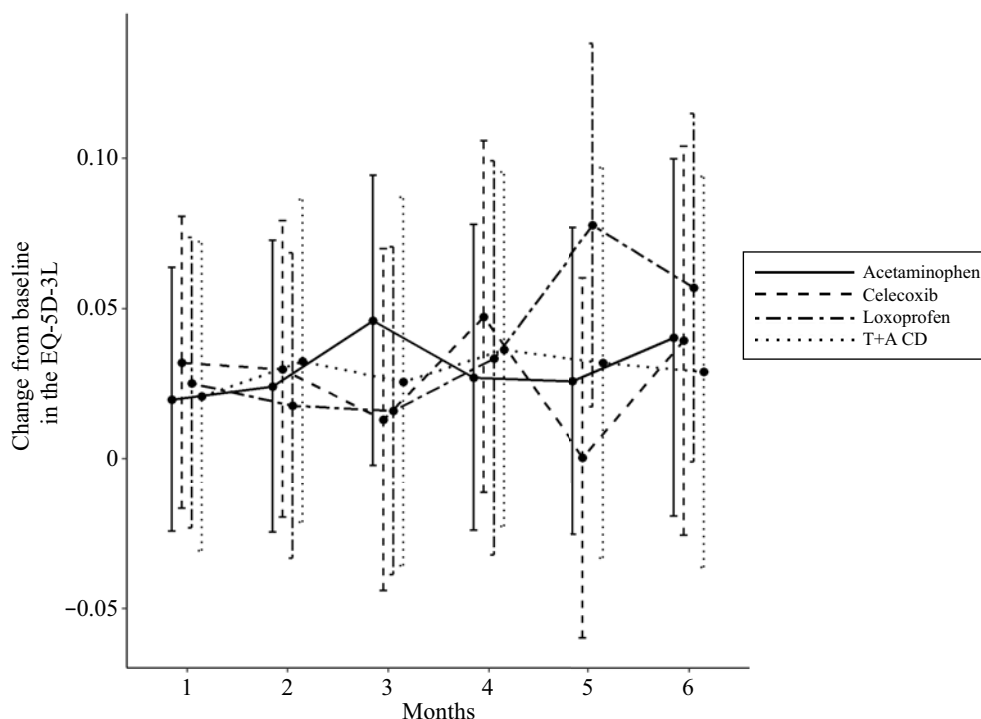
After six months of treatment, only the JOA score showed a significant difference among the four drugs (Fig. 2). The

JOA score includes subjective symptoms, such as LBP, leg pain, and activities of daily living. It also consists of an objective straight leg raising test or a manual muscle test, which is not used exclusively for evaluating LBP, but is also used to assess lumbar disease with sciatica. According to the JOA score, acetaminophen was the most effective of the four drugs throughout the six-month follow-up period. The largest effect size of  $>3$  points suggests acetaminophen had





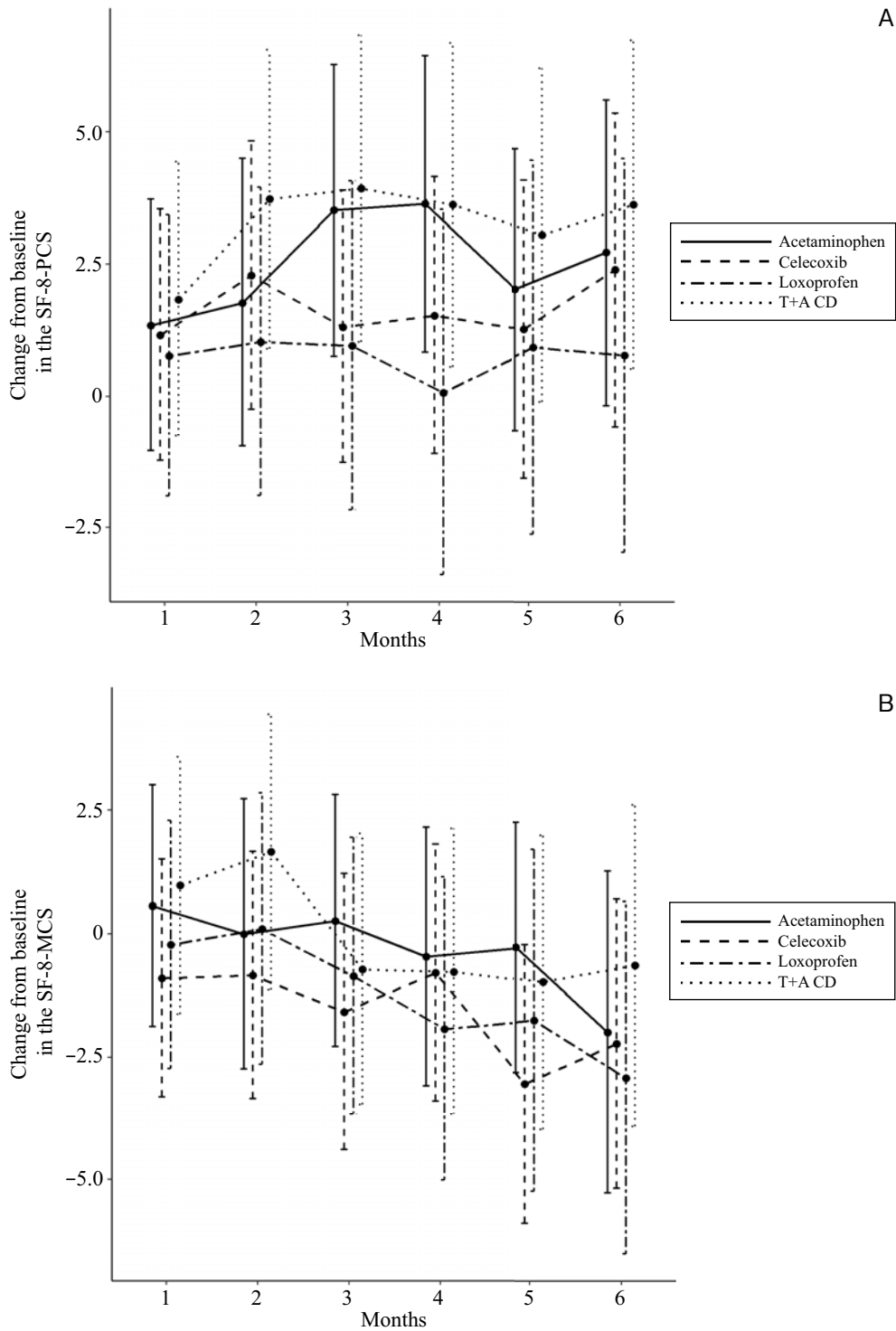
**Figure 4.** Change from baseline in the RDQ total score during the follow-up period. Error bars represent 95% confidence intervals. Abbreviations: CD, combination drug; RDQ, Roland–Morris Disability Questionnaire; T+A, tramadol and acetaminophen



**Figure 5.** Change from baseline in the EQ-5D-3L score during the follow-up period. Error bars represent 95% confidence intervals. Abbreviations: CD, combination drug; EQ-5D-3L, EuroQol five-dimensions three-levels; T+A, tramadol and acetaminophen

a comprehensive effect both for pain intensity and functional impairment. It is surprising these results were achieved by a mean dose of 1,200 mg, much lower than the international

standard dose of 4,000 mg. The acetaminophen dose is relatively low because a maximum daily dose of 4,000 mg and a one-time dose of 1,000 mg as used abroad were permitted



**Figure 6.** Change from baseline in the SF-8 score during the follow-up period. Error bars represent 95% confidence intervals. (A) PCS score, and (B) MCS score.

Abbreviations: MCS, mental component summary; PCS, physical component summary; SF-8, Short Form 8-item health survey; T+A, tramadol and acetaminophen

in 2011, and a higher dose might be prescribed in Japan now<sup>13</sup>). Even against such a background, at six months, besides the VAS for LBP, which improved equally in all groups, the LBP subscale of JOABPEQ or RDQ showed relatively smaller improvement. These results suggest that acetaminophen’s significant superiority in the JOA score might not be due to the reduction of pain intensity alone be-

cause the JOA score is not a pure subjective pain measurement. Additionally, although acetaminophen’s effectiveness is reported as dose-dependent<sup>22</sup>), we could not compare the dose of acetaminophen between patients with or without treatment effectiveness, and a deviation of the dose might affect the results. Further evaluation of acetaminophen usage for CLBP is expected. The other outcome measures showed

no significant differences from baseline at one and six months.

Overall, most of the outcome measures, including VAS for LBP, JOABPEQ, RDQ, EQ-5D, and PCS of SF-8, tended not to show monthly cumulative effectiveness between the four drugs an almost equivalent effect of these four drugs for the treatment of CLBP. The JOA Clinical Practice Guidelines on the Management of LBP indicate pharmacological treatment effectively reduces pain intensity and improves function and is therefore highly recommended<sup>9</sup>. Also, our previous data demonstrated that treatment using these four drugs for CLBP was cost-effective<sup>10</sup>. Although the four drugs' differences were limited in this study, all four drugs have shown an adequate treatment effect of up to six months despite a relatively better clinical improvement indicated with acetaminophen.

There are several limitations to this study. One is based on study design, because there was no random assignment of patients to treatment, and prescriptions were not regulated or standardized. Instead, individual physicians used their discretion to decide who could participate and which drug to prescribe. Second, we had no information about what kinds of medication had been used previously and how long. A drug chosen for use in this study may have been prescribed because pharmacological treatment with other drugs failed due to insufficient effectiveness or side effects. Third, we did not define the pathology or location of LBP in detail. In the inclusion criteria for the present study, CLBP was defined when an LBP persisted  $\geq 3$  months. Clinically, the severity of degenerative changes might affect treatment effectiveness, although the influence of the severity of the changes was not evaluated. Analyses include different pathologies such as vertebral fracture, spondylosis, and/or structural spinal deformities like scoliosis or kyphosis. These factors were adjusted statistically for the multivariate analysis, as were other background factors shown in Table 2. Further evaluation of the pathology for which pharmacological treatment is preferable is warranted. The high discontinuation rate, which approached 50% by six months, must be acknowledged concerning our study. We were unable to evaluate the reasons for discontinuations. However, in some populations, pharmacological treatment with one of the four drugs could well have failed due to insufficient effectiveness or side effects. Despite the limitations above, importantly, this study's results pertain to an original nationwide, multi-center, prospective study. A study of this nature has never been performed in Japan to our knowledge. Based on the present results, further evaluations should be performed with updated materials and methods in the future.

## Conclusions

This nationwide study project revealed that the only significant differences among the four drugs investigated in this study concerned the mental health subscale of JOABPEQ at one month and the JOA score at six months. Acetaminophen

exhibited a statistically superior effect in one outcome measure at each of the two-time points. However, the other drugs were also effective for the treatment of CLBP. We uphold the view that multiple outcome measures should be used to elucidate differences in treatment effects and ensure that relatively small differences in patients' status are considered more comprehensively. More thorough evaluations using multiple outcome measures that can compensate for any potential shortfalls attributable to one measure or another appear to represent a preferable approach to the evaluation of CLBP. This complex pathology includes abnormal conditions of both the body and mind.

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