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ORIGINAL RESEARCH ARTICLE

Estimating Prevalence and Healthcare Utilization for Treatment-Resistant Depression in Japan: A Retrospective Claims Database Study

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Abstract

Background Major depressive disorders (MDDs) including treatment-resistant depression (TRD) are common disabling conditions, but data on their epidemiology in Japan are limited. This study investigated the incidence, epidemiology, and direct medical costs of TRD and pharmaceutically-treated depression (PTD) in Japan to increase our health economic understanding of this phenotype of MDD.

Methods A retrospective cohort study from a private health insurance claims database estimated the 1-year incidence of PTD and TRD and described the health services used and direct medical costs associated with these conditions.

Results In the year from 1 April 2012 through 31 March 2013, we identified 1143 incident PTD cases among 98,552 eligible subjects, i.e. 11.59 cases/1000 patient-years. Of the PTD patients, 51.4% were women. Within the 1-year observation interval 137 patients failed more than two antidepressive treatment approaches and thus developed TRD. Though co-morbid conditions and age were similar among PTD and TRD patients, medical costs per patient (patient-year) during their treatment intervals were 1.01 million JPY (0. 540 million JPY) in the TRD population and 0.643 JPY million JPY (0.645 million JPY) in the PTD population who did not convert into TRD.

Conclusions This study describes the PTD and TRD patient populations in a large claims database in Japan and highlights an unmet medical need for the treatment of TRD to provide better preventative measures and interventions for the treatment of depression.

Key Points

This is the first database study to explore prevalence and associated healthcare utilization and treatment costs of treatment-resistant depression in Japan.

Our findings suggest that patients suffering from treatment-resistant depression cause higher healthcare costs per episode compared with patients with depression that is not treatment resistant.

1 Background

It is estimated that more than 300 million people worldwide suffer from major depressive disorder (MDD) [1], and that by 2020, major forms of depression will become the second leading cause of global disease burden after ischemic heart disease [2]. Depression is a current public health concern because of its early-age of onset, high prevalence, high impact on patient quality of life and ability to function, as well as high clinical and economic burden [3]. Depression can occur at any point during an individual's lifetime and is characterized by a single or

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recurrent episode of clinically diagnosed depressive symptoms with variations during each episode. It is the most common severe psychiatric illness and affects emotions, thought, and behavior, leading to low disease-related quality of life. The incidence of suicide attempts is about 20- to 40-fold for patients suffering from an MDD episode [4], making suicide the second leading cause of death among 15- to 29-year-olds globally [5]. Japan has one of the highest suicide rates worldwide [6].

Although depression can be treated pharmacologically, studies in the USA [7] and UK [8] reported that a substantial subset of depression patients, termed treatment-resistant depression (TRD) patients, do not achieve an adequate clinical response to the administration of antidepressants. The current definition of TRD lacks consensus; however, the Committee for Medicinal Products for Human Use at the European Medicines Agency defines TRD as pharmacologically-treated depression (PTD) that does not show clinically meaningful improvement after at least two different antidepressant medications used for a sufficient length of time at an adequate dose with adequate affirmation of treatment adherence [9].

Large longitudinal studies suggest that MDD patients who develop treatment resistance have a low chance to achieve response or remission with each subsequent line of treatment [10]. Although TRD patients have been characterized well in regard to their clinical characteristics, including co-morbidities, there is a paucity of data with regard to the epidemiological and health economic consequences in Japan. Furthermore, the burden of TRD in terms of disability, cost, human suffering and suicide is unclear [11] because the accurate and systematic assessment of TRD, including predictive utility and reliability of TRD staging, is difficult [12]. Usually, response is defined as a reduction in depressive symptoms to $<50\%$, and remission as a full recovery [13].

From a US economic viewpoint, patients with TRD generate higher direct medical costs compared with those with MDD within a 12-month time horizon [14] and have higher indirect productivity costs from a societal point of view [15]. One reason for this difference in economic burden is the increased number of co-morbidities in TRD patients compared with non-TRD patients [16]. In addition, secondary administrative data indicated that some patients are treated with up to four different pharmacological treatments still fail to respond to treatment, and thus have higher healthcare utilization and higher per-patient medical costs [17].

The estimated lifetime prevalence of MDD in the USA is 16.2% [18], and the 12-month prevalence is 6.7% [19]. Estimations about the rate of patients developing TRD vary widely from 6.6 [7] to 35% [20] of MDD patients. For Japan, the lifetime and 12-month prevalence rates of MDD were estimated as 3–7 and 1–2%, respectively [21]. Interestingly, patients with depression in Japan were reported to be less likely to seek medical treatment or consult a psychiatrist compared with patients in Western countries [21], and the lack of utilization of mental health services was not related to gender, age or income level. Furthermore, an international WHO report indicated that in Japan the majority of people recently diagnosed with a psychiatric disorder do not seek mental healthcare or use other support systems [22]. However, no longitudinal cohort studies are available for Japan that would allow a good estimation of TRD rates and related costs. The aim of this study was therefore to estimate the incidence, the amount of medical services used, and the direct costs of PTD and TRD, through a retrospective analysis of a health insurance claims database and thus help improve our understanding of the socioeconomic impact of TRD in Japan.

2 Methods

2.1 Data Source

Health insurance claims data from non-governmental employees and their family members between July 2009 and March 2015 sourced from multiple health insurance associations were retrieved from the Japan Medical Data Center (JMDC). During this period, a total of 2,958,220 patients were enrolled in the JMDC database. The database provides comprehensive patient and clinical information, including patient demographics, diagnostic codes, dates and types of procedures, dispensed prescription drugs, medical services provided to inpatients and outpatients, and expenditures. The JMDC database has been used to investigate a wide range of conditions in Japan such as schizophrenia [23] or cardiovascular disease [24]. All personally identifiable information was de-identified to protect patient privacy. Therefore, no informed consent was necessary.

2.2 Selection of Study Population

A retrospective cohort design was used. JMDC database members joined the study cohort on 1 April 2012 if they were within 18–60 years of age (i.e., were born between 1952 and 1994), had no prior depression diagnosis (ICD 10; F32.x, F33.x, F34.1, F41.2, F43.2, F53.0), no previous diagnoses of other mental diseases (ICD 10; F0;F1;F2;F3F20; F30;F31), and no prior prescription of any antidepressant medication before 31 March 2012. Antidepressant medication was defined as a medication that is approved for the treatment of depression in Japan. The list of antidepressant medications can be found in

Supplementary Table 1. Patients were censored if they develop other psychiatric conditions as mentioned above after they were included in the study cohort.

Based on these criteria, 98,552 patients who were continuous JMDC database members from 1 April 2012 through 31 March 2013 were included in this analysis (Table 1). Maximal follow-up time was until 31 March 2015.

2.3 Identification of a Pharmaceutically Treated Depression (PTD)

A pharmaceutically treated depression (PTD) treatment interval began when a study subject received a depression diagnosis and simultaneously or subsequently (within less than 30 days) a dispensation of an antidepressant medication.

The start of a treatment interval was the date of depression diagnosis or the date of antidepressant medication dispensation, whichever was earlier. A treatment interval was terminated when the subject received no depression diagnosis and was dispensed no antidepressant medication for 120 days. The duration of a PTD interval was defined as the number of months from PTD index month to the month a treatment interval ends. It is important to recall that what we call a treatment interval of PTD is a sequence of dispensing of antidepressant medications and visits with a depression diagnosis, and that this represents a treatment interval of care for PTD rather than a clinical episode of clinical depression. In particular, medication may include some prophylaxis.

2.4 Identification of Treatment-Resistant Depression (TRD)

A TRD treatment interval is a PTD treatment interval in which two treatment regimens have failed. A treatment regimen fails when, at least 15 days after it began, an antidepressant medication is added or substituted for another medication. We assumed 15 days as adequate threshold, because evidence suggest that nonresponse is predicted by a lack of symptom improvement during the first 14 days of therapy [25]. Moreover, this is a common definition used in database analysis and choosing this threshold value allows for a better comparability across database studies [26].

As we are not able to observe symptom improvements in claims databases, we acknowledge that there is some uncertainty around this definition.

2.5 Resource Utilization

Hospital claims were characterized by resource utilizations as: hospitalization in emergency department, hospitalization in psychiatric emergency department, psychiatric hospitalization, all hospitalizations, psychiatric office visit (out-patient), and office visit (out-patient). Total cost per patient and total cost per patient-year were calculated. Cost per person-time and cost per person capture of different information and the former measure adjusts for time while the latter does not. Total cost refers to the sum of costs paid by insurance and by the patients via co-insurance schemes and that are paid out of pocket. The co-insurance rate is 30% for people under 70 years of age and 20% for those above 70 years of age. Maximum co-payments are capped depending on household income ranging from 35,400 JPY (US$307) per month for the population earning less than 1 million (US$8700) a year to 252,600 JPY per month (US$2200) for those with an annual income above 11.6 million JPY (US$100,900). Once a person turns 70 years old, the upper limit of the co-payments is reduced drastically ranging from 8000 (US$70 USD) to 80,000 JPY (US$700) per month depending on income and whether the cost is related to in-patient or out-patient services. At the age of 75 years, everyone in Japan switches to an insurance scheme for the elderly that was established 2008. The common co-payment rate for this plan is 10% [27]

2.6 Statistical Analysis

This study employed a cohort design because TRD is defined by a temporal sequence of events (unsuccessful treatment regimens) that may occur in a subject with PTD. A cohort perspective also facilitates estimation of TRD incidence and duration of treatment. This was a descriptive study so no effect measure was calculated. The incidence of PTD and TRD were estimated by proportion per year.

Table 1 Selection of subjects

Criterion	Number of patients
All database members	2,958,220
Born between 1952 and 1994	2,092,248
Continuously enrolled between Dec 2011 to Mar 2012	130,339
Do not have depression diagnosis or antidepressant medication dispensing before Mar 2012	101,357
No exclusion diagnosis before Mar 2012	101,006
Database member after Apr 2012 eligible for study cohort	98,552

Group comparisons were conducted using the Kruskal–Wallis test with post hoc Scheffe's rank sum multiple contrast tests. All statistical analyses were performed using R version 3.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Incidence and Patient Characteristics

In total, 1143 (1.2%) subjects experienced 1154 PTD treatment intervals for the 98,552 patients contained in the selected sample (Table 1). Of the patients who met the inclusion criteria for PTD, 11 patients had more than one treatment interval during the study period (Table 2). If a patient had at least one TRD treatment interval, the patient was classified as a TRD patient. Reasons for censoring among subjects with PTD but not TRD and among subjects with TRD are shown in Table 2.

One hundred and thirty-seven patients developed TRD within 1 year. TRD and non-TRD/PTD patients (i.e., patients with PTD who did not develop TRD) were of a similar mean age (43.4 and 42.8 years, respectively) (Table 3). Among patients with PTD (whether or not they developed TRD), 556/1143 (48.6%) were male. In contrast, among those with TRD, 84/137 (61.3%) were male. TRD treatment intervals had longer durations (mean 22.0 months, median 25.0 months) than did PTD intervals without TRD (mean 11.0 months, median 7.0 months).

Table 2 Incidence of PTD and TRD

Incident PTD between Apr 2012 to Mar 2013	1143
PTD episode censored without TRD	1006
Incident TRD	137
Incident TRD episode not censored	94
Incident TRD episode censored	43
Reasons for censoring among subjects with PTD but not TRD	
End of study	705
Left database	230
Diagnosis of psychosis	39
Diagnosis of mania	5
Diagnosis of bipolar disorder	27
Reasons for censoring among subjects with TRD	
End of study	94
Left database	27
Diagnosis of psychosis	6
Diagnosis of mania	1
Diagnosis of bipolar disorder	9
Diagnosis of dementia	0

AD antidepressants, *PTD* pharmaceutically-treated depression, *TRD* treatment-resistant depression

3.2 Healthcare Utilization and Medical Costs

3.2.1 Medication

The antidepressant classes most commonly used were selective serotonin reuptake inhibitors (SSRIs) followed by sulpiride instead of serotonin and noradrenaline reuptake inhibitors (SNRIs) (Table 4). Sulpiride has been approved for the treatment of depression in Japan (150–300 mg/day dose).

It is apparent from the table that patients received more than one antidepression medication simultaneously. For example, the second treatment line in the TRD population consists of 264/137 = 1.92 antidepression medications per patient on average.

3.2.2 Medical Service Utilization

In all groups, there were few psychiatric emergency hospitalizations and there were none among newly developed TRD patients. Patients with non-TRD/PTD had more hospitalization days per person years than TRD patients or subjects without PTD (3.857 vs. 1.837 vs. 1.715 days/patient-years) ($p < 0.05$), TRD patients had slightly more psychiatric hospitalization days/person years than non-TRD/PTD patients or subjects without PTD (0.895 vs. 0.808 vs. 0.010 days/patient-years) ($p < 0.0001$).

The number of psychiatric office visits per patient-years among TRD patients was much greater than for non-TRD/PTD patients or subjects without PTD (17.370 vs. 8.528 vs. 0.156 /patient-years) ($p < 0.0001$). The trend was similar but much less pronounced for all office visits (TRD vs. non-TRD/PTD vs. non PTD: 45.537 vs. 37.019 vs. 21.224/patient-years) ($p < 0.0001$). For non-PTD patients service utilization is much smaller in all categories (Table 5).

3.2.3 Medical Costs

Medical costs in millions of yen per patient were 1.014 for those with TRD, 0.643 for those with PTD but not TRD, and 0.327 for the non-PTD population. Expressed in millions of yen per patient-year, the total direct medical cost of TRD is 0.540 million yen, and for non-TRD/PTD it was 0.645 million yen. This compares to 0.361 million yen for the non-PTD group (Table 5) ($p < 0.0001$). The difference between the cost per patient (which is similar to the cost per treatment interval) and the cost per patient-year stems from the different treatment durations, which are significantly longer in TRD patients. This reduces the cost when reported as cost per time unit. We report both measures because for reimbursement decision makers, the cost-per-patient approach is probably more relevant since this is the kind of cost policy makers need to deal with when it comes to budget allocation decisions.

Table 3 Description of study subjects and depression episodes by depression type, sex, age group, and co-morbidities

Characteristic	All subjects		PTD subjects		PTD subjects excl. TRD		TRD subjects		PTD treatment intervals		PTD treatments intervals excl. TRD		TRD treatment intervals	
Number	98,552		1143		1006		137		1154		1016		137	
Age (years)[a]														
Mean	44.7		43.4		43.4		42.8		43.3		43.4		42.8	
SD	10.9		10.5		10.6		9.2		10.5		10.6		9.2	
Median	46.0		45.0		45.0		44.0		45.0		45.0		44.0	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Male age groups (years)	47,242	100%	556	100%	472	100%	84	15%	561	100%	477	100%	84	100%
18–29	4254	9.00%	51	9.20%	45	9.50%	6	1.10%	52	9.27%	46	9.64%	6	7.10%
30–39	7050	14.90%	107	19.20%	89	18.90%	18	3.20%	109	19.43%	91	19.08%	18	21.40%
40–49	14,113	29.90%	209	37.60%	171	36.20%	38	6.80%	211	37.61%	173	36.27%	38	45.20%
50–60	21,825	46.20%	189	34.00%	167	35.40%	22	4.00%	189	33.69%	167	35.01%	22	26.20%
Female age groups (years)	51,310	100%	587	100%	534	100%	53	100%	593	100%	539	100%	53	100%
18–29	6364	12.40%	91	15.50%	82	15.40%	9	16.98%	92	15.51%	83	15.40%	9	17.00%
30–39	12,645	24.60%	146	24.90%	133	24.90%	13	24.53%	146	24.62%	133	24.68%	13	24.50%
40–49	14,724	28.70%	159	27.10%	140	26.20%	19	35.85%	162	27.32%	143	26.53%	19	35.80%
50–60	17,577	34.30%	191	32.50%	179	33.50%	12	22.64%	193	32.55%	180	33.40%	12	22.60%

[a] Age at onset of episode

PTD pharmaceutically-treated depression, *SD* standard deviation, *TRD* treatment-resistant depression

Table 4 Classes of antidepressant medications used to treat PTD and TRD

Medication class	TRD population			PTD population without TRD	
	1st regimen ($n = 137$) (%)	2nd regimen ($n = 137$) (%)	3rd regimen ($n = 137$) (%)	1st regimen ($n = 1016$) (%)	2nd regimen ($n = 226$) (%)
SSRI	80 (58.4)	94 (68.6)	94 (68.6)	424 (41.7)	124 (54.9)
Sulpiride	64 (46.7)	71 (51.8)	53 (38.7)	309 (30.4)	59 (26.1)
SNRI	19 (13.9)	34 (24.8)	38 (27.7)	154 (15.2)	57 (25.2)
NaSSA	16 (11.7)	16 (11.7)	19 (13.9)	82 (8.1)	29 (12.8)
TrCA	11 (8.0)	23 (16.8)	29 (21.2)	127 (12.5)	35 (15.5)
TeCA	3 (2.2)	5 (3.6)	7 (5.1)	17 (1.7)	32 (1.3)
Others	12 (8.8)	21 (15.3)	20 (14.6)	56 (5.5)	12 (5.3)
Total	205 (149.6)	264 (192.7)	260 (189.8)	1169 (115.1)	319 (141.2)

NaSSA noradrenergic and specific serotonergic antidepressant, *PTD* pharmaceutically-treated depression, *SNRI* serotonin and noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TeCA* tetracyclic antidepressant, *TrCA* tricyclic antidepressant, *TRD* treatment-resistant depression

4 Discussion

4.1 Incidence

Our study estimated the 12-month incidence of PTD as 1.2% for the privately insured population of Japan. Recent epidemiologic studies of community residents reporting the prevalence of major depression according to DSM-IV criteria was 1–2% for 12 months and 3–7% for lifetime in Japan [28]. The estimated differences between Japan and the USA or other Western countries may be partially due a greater reluctance to report depression among people in the Japanese population than in Western countries. Compared to Western countries, Japanese patients with depression were reported to have decreased behaviors of seeking any medical treatment or of consulting a psychiatrist (27% sought any; 14% consulted a psychiatrist), which is lower than that reported from many Western countries, and

Table 5 Medical services used by people during PTD episodes (with and without TRD) and by people without PTD

	Subjects with TRD			Subjects with PTD but not TRD			Subjects without PTD within first year		
Count (*n*)	137			1006			97,409		
Person years (PY)	257			1003			88,154		
	Total	Total/subject	Total/PY	Total	Total/subject	Total/PY	Total	Total/subject	Total/PY
Hosp. days, psychiatric	230	1.679	0.895	810	0.805	0.808	878	0.009	0.010
Hosp days, all	472	3.445	1.837	3869	3.846	3.857	151,220	1.552	1.715
Psy. Emer. Dep., days	0	0.000	0.000	145	0.144	0.145	194	0.002	0.002
Emer. Dep., days	32	0.234	0.125	48	0.048	0.048	2,038	0.021	0.023
Psy. OV	4,464	32.584	17.370	8554	8.503	8.528	13,708	0.141	0.156
OV	11,703	85.423	45.537	37,130	36.909	37.019	1,870,988	19.21	21.224
Total costs (million Yen)	138.900	1.014	0.540	646.600	0.643	0.645	31,862.000	0.327	0.361

Emer. Dep. emergency department, *Hosp.*, any hospitalization, *OV* any office visit, *Psy. Emer. Dep* emergency hospitalization to the psychological department, *Psy. OV* office visit for psychological treatment, *PTD* pharmaceutically-treated depression, *PY* patient-year (/1,000 patient-years), *TRD* treatment-resistant depression

Reported values are not age- or gender-adjusted

approximately half of that in the USA [28]. Accordingly, previous epidemiological studies have shown a lower prevalence of depression in East-Asian countries including Korea, Japan, and China compared with the West [29]. Findings from the World Mental Health Japan Survey 2002–2003 [21] for instance suggest that the majority of people with a recent psychiatric disorder did not utilize mental healthcare or other support systems, despite service improvement over time. Such cross-cultural differences would equate to a higher diagnostic threshold for depression in East-Asian countries [30, 31]. Presumably, these cultural differences might also influence the gender effects on depression. Considering Japan is in the East-Asian sociocultural realm, similar estimates after accounting for sociocultural differences may be anticipated for this study. Similar to the global trend, women exhibited a greater risk than men for depressive disorders in Japan, although age and social class distributions were different from other countries [32]. Twelve percent of PTD patients developed TRD within a year, which is in the range of estimates from other countries [4, 20, 33]. For Taiwan, which is culturally close to Japan, this proportion was estimated to be 21% [26]. As we utilized a database whose members include employees and their families, patients with a very severe history of depression might not be able to stay in employment and are therefore under-represented in this sample. This would imply a downward bias of the TRD incidence rate. The majority of TRD patients were male in our analysis, which is in contrast to findings from Taiwan [26] or the USA [7]. Again, the composition of our database might be a potential explanation for this finding.

4.2 Medication

Prescription patterns in the study population showed that SSRIs were the most frequently used drugs, similar to the usage reported for six other East-Asian countries (at 40 sites) [32]. In contrast, a similar study in the USA reported that SNRIs were most frequently used [7].

Another finding is the wide usage of sulpiride, which confirms results of previous studies [34]. A Japanese chart review for instance found that sulpiride was the most frequently prescribed antidepressant with a share of 40.3% in 367 outpatients with a major depressive disorder [35]. The wide use of sulpiride is somewhat unexpected given the limited evidence of its efficacy in depression. A review of the UK HTA agency NICE in 2011 identified only one clinical trial that found a statistically significant greater mean change in the 21-item Hamilton Depression Rating Scale with 150–300 mg sulpiride compared with placebo. NICE concluded that due to the small number of studies and lack of study quality assessment, the effectiveness of second-generation antipsychotics in the treatment of major depressive disorder is unclear [36]. Table 4 indicates that many subjects were receiving more than one medication for depression at a time, and sulpiride may have been used to augment an antidepressant. In a Japanese clinical trial, this has been recommended as a successful strategy for accelerating antidepressant response [37].

Our results also suggest that more than one antidepressant medication was prescribed on average, especially in the later treatment lines, although the link between polypharmacy and efficacy has not been established [38]

and polypharmacy is not recommended in international and Japanese guidelines. Instead, clinical guidelines recommend monotherapy with a second-generation antidepressant for acute-phase treatment [39]. Despite this, only 26% of Japanese psychiatrists treat patients with monotherapy according to a survey by Ueshima et al. [40]. A Japanese claims database analysis of 7,338 Japanese patients with depression also observed various patterns of polypharmacy [41].

4.3 Healthcare Utilization and Medical Cost

Some psychiatric service utilization including psychiatric hospital days, overall office visits, and psychiatric office visits for TRD patients was higher compared to PTD without TRD and compared to patients without PTD. This is partly due to the fact that when a patient had a prescription renewed, that event was considered to be an outpatient visit. The finding of increased service utilization of the TRD population holds for both the per-patient-year and per-patient perspective, and echoes recent findings from Brazil [42] or the USA [4]. No similar difference was seen for all types of hospital days, where PTD patients who were not TRD had higher resource utilization.

Total treatment costs per person among TRD patients of 1.01 million JPY were higher than for patients who only exhibited PTD (0.643 million JPY) or compared with the non-PTD population (0.327 million JPY per patient). Those are only direct medical costs that accrue to the health insurer and a recent health economic study found that direct medical costs constitute only 14.2% of the total cost associated with depression in Japan [43]. The biggest fraction of the economic burden resulted from indirect costs such as productivity losses [44]. Although the magnitude of healthcare expenditure/costs for TRD was smaller than that reported in the USA [7], this study shows the same directionality. That treatment costs are higher in the USA is a well-established result in the literature and the cited Japanese health economic study [44] found direct treatment costs to be only 50% of those in the USA [45]. That TRD patients do incur higher costs to the healthcare system has been reported for a number of other countries such as Brazil [42] or the USA [14, 46–48].

4.4 Limitations

This study had some limitations. The study's definition could not take dosage into account when defining antidepressant medication regimens due to substantial amounts of missing data, which is likely to affect the estimated TRD incidence. However, by not using dosage as a factor, this allows more regimens to be counted and thus would capture more cases compared with a study that imposed a dose requirement. Moreover, this study only investigated pharmacological interventions among patients with depression. The role of non-pharmacological treatments, such as psychotherapy, was not investigated here. For that reason, the estimates from this study are likely to be a lower bound for the actual disease incidence. On the other hand, psychotherapy is only rarely prescribed in Japan compared to its wide use in the USA [49]. Another potential limitation is that claims were used as the basis of defining events for analysis of study. In clinical practice, prophylactic measures of continued antidepressant prescriptions are taken because those that have had episodes of depression are at increased risk for sequential episodes [45, 50]. Prophylactic treatment behavior would be indistinguishable from ongoing clinical depression, so some of the changed regimens may have been initially effective. This may have affected the estimates of the durations of episodes of PTD and TRD and caused some PTD cases that were not TRD to be misclassified as TRD cases. This misclassification would result in an overestimation of the incidence of TRD. However, this limitation is common in retrospective database studies of TRD and is difficult to avoid. Measurement of patient-reported outcomes or physician assessment, such as the antidepressant treatment response questionnaire (ATRQ) or Mini International Neuropsychiatric Interview (MINI) for treatment response, would not have been available in claims data. Future studies should validate the findings using alternative definitions of TRD in order to address the high degree of uncertainty there is surrounding our results. Moreover, a common problem in any database analysis is the coding quality [51]. More often than not, hospitals or physicians designate medical codes that provide the highest reimbursement rates, but disease codes do not always reflect clinical reality.

5 Conclusions

To the best of our knowledge, this study provides the first population-based estimates for the incidence and related costs of TRD in the Japanese population. The unmet need for better treatment of depression and the high cost of depression indicate a need for both society and the affected individuals for better means of prevention and treatment of depression.

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Compliance with Ethical Standards

This was a retrospective database study; the authors were not involved in the collection of this data. Retrieval of the data from this database occurred in an unlinked fashion. As the data had been

anonymized, the Ethical Guidelines for Epidemiological Research (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare of Japan), which require ethics approval and informed consent, are not applicable to this study. Based on the Ethical Guidelines on Biomedical Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare of Japan), pharmacoepidemiological studies conducted on medical databases constitute research carried out on pre-existing material and information, that did not require any interventions or interactions with patients. For such studies, including this study, obtaining written informed consent from patients is not compulsory.

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Conflict of interest JM, ST, and WF are employed by Janssen.

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