Investigation into changes in prescription of psychotropic drugs after introduction of polypharmacy reduction policy and influence of psychotropic polypharmacy on safety events based on large-scale medical databases

Yoko Hirano

DP-17403

Graduate School of Pharmaceutical Sciences

Department of Clinical Medicine (Pharmaceutical Medicine)

Kitasato University

5-9-1 Shirokane, Minato-ku, Tokyo, 108-8641, Japan

Abstract

Psychotropic polypharmacy is common in clinical practice despite its limited supporting evidence. In Japan, polypharmacy reduction policy, which reduces the reimbursement of medical cost, has been introduced to address unnecessary psychotropic polypharmacy. The rule was applied to the prescriptions of 3 or more anxiolytics or 3 or more hypnotics in the policy introduced in 2012. The prescriptions of 4 or more antidepressants or 4 or more antipsychotics were added to the rule in the policy revised in 2014. Furthermore, the prescriptions of 3 or more drugs of anxiolytics, hypnotics, antidepressants, or antipsychotics were subject to the reduction criteria of the policy revision in 2016. Some benzodiazepine receptor agonists (BZs) are classified as anxiolytics and others are as hypnotics although they have similar mechanisms of action.

In this study, first, changes in psychotropic prescriptions after the introduction and revisions of the polypharmacy reduction policy were examined using two large-scale Japanese medical databases; MinaCare database (MinaCare Co., Ltd., Tokyo, Japan) and Medical Data Vision (MDV) database (Medical Data Vision Co., Ltd., Tokyo, Japan) (Research 1). Second, the influence of psychotropic polypharmacy on safety events was examined using the MinaCare database (Research 2). Hypertension, diabetes mellitus, pneumonia, extrapyramidal syndromes (EPS), hyperlipidemia, bone fracture, and acute myocardial infarction were selected for the safety events of interest.

In Research 1, the effect of the policy reducing the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics was identified, but not in BZs. On the other hand, there was no clear and consistent tendency of decrease in the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics in the inpatients. This might be due to the fact that

the policy was not applied to the inpatients. Only limited effects were seen for increasing the proportions of monotherapy and reducing the proportions of patients above clinically recommended doses. Moreover, the proportion of patients with nonpharmacological treatments was much lower than that with psychotropic prescriptions. There was no noticeable issue in psychotropic prescriptions specific for the elderly.

In Research 2, all categories of psychotropic drugs (anxiolytics, hypnotics, antidepressants, and antipsychotics) were significantly associated with EPS, and the tendency was stronger as the number of prescribed drugs was increased. A clearer association between polypharmacy of BZs and EPS was indicated. It was suggested that prescription of 2 or more BZs was associated with hyperlipidemia. In the analyses by subclasses of the psychotropic drugs, BZs, tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, and typical and atypical antipsychotics were significantly associated with EPS, and SSRIs and atypical antipsychotics were significantly associated with hyperlipidemia. In addition, high-dose prescription of the psychotropic drugs might increase the risk of EPS. These results indicated that some safety events whose risk increases are associated not only with the number of drugs but also with total doses and drug subclasses.

In the polypharmacy reduction policy for the psychotropic drugs, the reduction rule was applied only to the number of drugs, not to the total doses. In addition, BZs were separately classified as anxiolytics or hypnotics. Based on our two researches, it was suggested that the rule considering total doses and drug subclasses including BZs in addition to the number of prescribed drugs should be taken into account. In addition, environmental improvement for expanding alternative nonpharmacological treatments would be needed.

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Abbreviations

ASR	adjusted sequence ratio
BAR	barbiturate and non-barbiturate
BZ	benzodiazepine receptor agonist
CBT	cognitive behavioral therapy
CI	confidence interval
CSR	crude sequence ratio
DPC	Diagnosis Procedure Combination
EPS	extrapyramidal syndromes
GABA	Gamma-aminobutyric acid
ICD-10	International Classification of Diseases, 10^{th} revision
MDV	Medical Data Vision
MIHARI	Medical Information for Risk Assessment Initiative
NSR	null-effect sequence ratio
PDPS	Per-Diem Payment System
SD	standard deviation
SNRI	serotonin norepinephrine reuptake inhibitor
SSA	sequence symmetry analysis
SSRI	selective serotonin reuptake inhibitor

1. Introduction

Psychotropic drugs such as anxiolytics, hypnotics, antidepressants, and antipsychotics are commonly prescribed in the treatment of mental and behavioral disorders [1]. Psychotropic polypharmacy is also common in clinical practice [2–4]. Mojtabai et al. reported that the proportion of patients with 2 or more psychotropic drugs increased from 42.6% to 59.8% from 1996-1997 to 2005-2006 in office-based psychiatry practices in the United States [2]. Their study reported that the proportions of patients with 2 or more drugs of sedative-hypnotics, antidepressants, and antipsychotics within the drug category in 2005-2006 were 17.8%, 25.4%, and 14.9%, respectively [2]. In Japan, the proportions of patients with 2 or more drugs of anxiolytics, hypnotics, antidepressants, and antipsychotics within the drug category were reported as 16.4%, 27.3%, 34.7%, and 30.0%, and those of 3 or more drugs were reported as 1.9%, 6.1%, 8.9%, and 8.5% based on claims data from Japan Medical Data Center's database in 2009 [5]. In addition, there is a report that the proportion of patients with 2 or more drugs of any anxiolytics or hypnotics was 54.6% in psychiatry and 20.4% in non-psychiatry based on claims data from Japanese National Database in 2011 [6]. All citizens and residents in Japan are covered by health insurance systems and most (70–90%) of drug fees are covered by their insurances, which seems to be one reason that polypharmacy is common in Japan. However, evidence supporting psychotropic polypharmacy is limited [3, 7–10]. Psychotropic polypharmacy increases the risk of adverse events and drug-drug interactions [2, 9, 11–16]. Several guidelines indicate that combination therapy (i.e., combination of several treatments including pharmacological and nonpharmacological treatments) and multiple prescription (i.e., prescription of 2 or more drugs within the drug category) are not standard therapy and

should be considered only if a patient's symptoms are moderate/severe or do not respond to an adequate dose and duration of a medication [17–19].

In Japan, polypharmacy reduction policy, which reduces the reimbursement of medical cost, was introduced in 2012 to address unnecessary psychotropic polypharmacy (Table 1) [20]. The reimbursement rate of the fee for continuous psychiatric outpatient services/consultation was reduced by 20% if 3 or more anxiolytics or 3 or more hypnotics were prescribed at one time in the policy introduced in April 2012. The policy was revised and tightened in October 2014 after the notification of the revision in April 2014, that is, antidepressants as well as antipsychotics were added to the fees reduction provision. The fee for continuous psychiatric outpatient services/consultation, prescription fees, and drug fees were not reimbursed or only partially reimbursed if 3 or more anxiolytics, 3 or more hypnotics, 4 or more antidepressants, or 4 or more antipsychotics were prescribed at one time. Furthermore, in April 2016, the policy was further tightened, and these fees were not reimbursed or only partially reimbursed if 3 or more anxiolytics, 3 or more hypnotics, 3 or more antidepressants, or 3 or more antipsychotics were prescribed at one time. Although these policy interventions had been performed continuously, there have been few reports which investigated the effect of the policy on prescription of the psychotropic drugs.

In this study, first, changes in psychotropic prescriptions after the introduction and revisions of the polypharmacy reduction policy were examined using two large-scale Japanese medical databases (Research 1). The effect of the policy on psychotropic prescriptions was examined using a large-scale Japanese healthcare claims database [MinaCare database, MinaCare Co., Ltd. (Tokyo, Japan)], which included mainly

company employees' and their family members' claims data and all prescriptions and medical procedures information covered by the health insurance system (Research 1-1). The executing rates of nonpharmacological treatments were also investigated as alternatives to pharmacotherapy. Nonpharmacological treatments in Japan are less common than those in Western countries, and we investigated their actual conditions and their changes after the revisions of the polypharmacy reduction policy. In addition, because the MinaCare database has a limitation that the elderly aged ≥ 75 years are not included, the trend in psychotropic prescriptions was supplementarily examined using another database [Medical Data Vision (MDV) database, Medical Data Vision Co., Ltd. (Tokyo, Japan)], which is a hospital-based composite database and includes enough elderly data (Research 1-2). The MDV database includes both outpatients' and inpatients' claims, administrative, and laboratory data provided by hospitals which use the Diagnosis Procedure Combination (DPC) /Per-Diem Payment System (PDPS) [21] in Japan. Second, the influence of psychotropic polypharmacy on safety events was examined using the MinaCare database (Research 2). There have been few pharmacoepidemiological studies which investigated the relationship between psychotropic polypharmacy and the occurrence of safety events although such information is useful to consider and develop policy interventions on psychotropic polypharmacy. Based on these researches, we discuss the points to be considered in future approach for psychotropic polypharmacy.

This study did not require ethical committee review in accordance with current ethical standards for epidemiological studies in Japan [22].

Table 1. Summary of polypharmacy reduction policy for psychotropic drugs

Item	Regular score [a]	2012 [b]	2014 [c]	2016 [d]
Fee for continuous psychiatric outpatient services/ consultation	55	Fee reduction by 20% if 3 or more anxiolytics or 3 or more hypnotics were prescribed.	A) The fee was not reimbursed if 3 or more anxiolytics, 3 or more hypnotics, 4 or more antidepressants, or 4 or more antipsychotics were prescribed (excluding temporary prescription).	B) The fee was not reimbursed if 3 or more anxiolytics, 3 or more hypnotics, 3 or more antidepressants, or 3 or more antipsychotics were prescribed (excluding temporary prescription, or in the case that prescription of 3 antidepressants or 3 antipsychotics was necessary for patients). C) Fee reduction by 50% if 3 or more antidepressants or 3 or more antipsychotics were prescribed (excluding the case of B).
Fee for hospital visit/ in-house psychotherapy	2012: max 700 2014 and 2016: max 600	No reduction	No reduction	Fee reduction by 50% if 3 or more antidepressants or 3 or more antipsychotics were prescribed.
Prescription fee for out-of hospital prescription	68	No reduction	Score: 30 (in the case of A)	Score: 30 (in the case of B)
Prescription fee for in-hospital prescription	42	No reduction	Score: 20 (in the case of A)	Score: 20 (in the case of B)
Drug fee	—	No reduction	Fee reduction by 20% of all drugs prescribed at the same time (in the case of A)	Fee reduction by 20% of anxiolytics, hypnotics, antidepressants, and antipsychotics (in the case of B)

max, maximum.

[a] Regular score in cases where the psychotropic prescription does not meet the fees reduction criteria. The amount of money (Japanese yen) by multiplying the score by 10 is charged. The patients pay copayments partially depending age and income and rest of the money is reimbursed by their insurance.

[b] The polypharmacy reduction policy for psychotropic drugs was introduced and enforced on 1 April, 2012.

[c] The first revision of the polypharmacy reduction policy was notified on 1 April, 2014 and enforced on 1 October, 2014.

[d] The second revision of the polypharmacy reduction policy was enforced on 1 April, 2016.

2. Research 1 Changes in prescription of psychotropic drugs after introduction of polypharmacy reduction policy

2.1 Background

The polypharmacy reduction policy was introduced in 2012 to address unnecessary psychotropic polypharmacy and revised and tightened in 2014 and 2016. Okumura et al. reported the effect of the polypharmacy reduction policy for anxiolytics and hypnotics, which took effect in 2012 and 2014 [23]. Their study used a database of out-of-hospital prescriptions for outpatients dispensed by community pharmacies, and thus could not evaluate in-hospital prescriptions dispensed by pharmacies inside the hospitals. The aim of the policy is to reduce unnecessary psychotropic polypharmacy. Hence, it is important to follow not only out-of-hospital prescriptions but also in-hospital ones. Moreover, their investigation period, which was between April 2011 and November 2014, seems to be too short to evaluate the effect of the policy revision in 2014, which took effect in October 2014. In this policy, some benzodiazepine receptor agonists (BZs) are classified as anxiolytics and others are as hypnotics although they have similar mechanisms of action (Appendix Table 1). BZs have high potential for tolerance, dependence, and misuse as well as adverse events such as cognitive impairment, accidents, and falls [24]. The tolerance for BZs causes the increase of their daily dosage [25], which might cause more dependence and adverse events. Hence, promotion of proper prescription and proper use of BZs is an urgent matter. However, the polypharmacy reduction policy in Japan had not had a reduction rule for the category of BZs before April 2018. In addition, high-dose prescription of the psychotropic drugs has been a problem in Japan [26, 27]. Especially, some studies indicate that Japanese patients receive higher doses of antipsychotics compared to

patients in other countries [28–30]. It is also important to address unnecessary high-dose treatment, but this policy had the reduction rule just for the number of drugs, not for total doses although the potency is different between drugs (Appendix Table 1). Furthermore, in the Japanese guidelines for major depressive disorders [31] and insomnia [32], nonpharmacological treatments such as cognitive behavioral therapy (CBT) and sleep hygiene education are recommended as the first-line therapy or combination therapy with pharmacological treatments.

In Research 1-1, the effect of the polypharmacy reduction policy on the prescriptions of 4 drug categories as well as BZs was examined from the point of view of the number of drugs and doses using the MinaCare database. The executing rates of nonpharmacological treatments were also investigated. In addition, in Research 1-2, the trend in psychotropic prescriptions was supplementarily examined using MDV database which includes enough elderly data.

2.2 Research 1-1 Investigation into changes in prescription of psychotropic drugs after introduction of polypharmacy reduction policy based on the MinaCare database

2.2.1 Methods

2.2.1.1 Data source

Research 1-1 was conducted using the MinaCare database. This database included about 5 million cumulative insured persons', mainly company employees and their family members' anonymized claims data provided by corporate health insurance societies. In this study, monthly administrative claims data including pharmacy claims, medical claims, and DPC claims between April 2011 and March 2017 in health

insurance societies that fully covered the investigation period were used. The database included information on patients' characteristics (encrypted personal identifiers, age, and sex), prescribed medications, medical procedures, and diagnoses. Pharmacy claims included the information of out-of-hospital prescriptions for outpatients dispensed by community pharmacies, and DPC claims included that of in-hospital prescriptions for inpatients hospitalized in the DPC hospitals. Medical claims included the information of in-hospital prescriptions for outpatients as well as in-hospital prescriptions for inpatients admitted to the hospitals other than the DPC hospitals dispensed by pharmacies inside the hospitals. Personally identifiable information such as patient name and exact date of birth were removed by the vendor before providing the data.

2.2.1.2 Study Population

Patients who were prescribed at least one psychotropic drug (anxiolytic, hypnotic, antidepressant, or antipsychotic) between April 2011 and March 2017 (study period) were defined as a study population. We included both prevalent and new users of psychotropic drugs because our study aimed to evaluate the effect of the policy on this entire population of patients. The classification of the psychotropic drugs was based on the Japanese polypharmacy reduction policy revised in 2016 (Appendix Table 1) [33].

2.2.1.3 Outcome Measures

The monthly utilizations of the psychotropic drugs were measured as total number of prescribed drugs in each month by drug category. The number of prescribed drugs was

counted based on generic names regardless of formulation.

In addition, average daily dose of the psychotropic drugs was calculated for each patient in each month by drug category and the mean of the average daily doses as well as the proportion of patients who were prescribed more than clinically recommended doses in Japan were calculated. For patients within or above clinically recommended doses, the means of the average daily doses were calculated in each month by the number of prescribed drugs in each drug category. Diazepam-equivalent doses for anxiolytics and hypnotics [34], imipramine-equivalent doses for antidepressants [35, 36], and chlorpromazine-equivalent doses for antipsychotics [37–41] were used (Appendix Table 1). The total of 15 mg/day (diazepam-equivalent dose) for anxiolytics and hypnotics, 200 mg/day (imipramine-equivalent dose) for antidepressants, and 450 mg/day (chlorpromazine-equivalent dose) for antipsychotics were defined as the upper limits of the clinically recommended doses based on the reference drugs' Japanese package inserts. For the analyses related to doses, the analysis in which anxiolytics and hypnotics were summed (i.e., sum of anxiolytics and hypnotics) was conducted because some BZs are classified as anxiolytics and others are as hypnotics, and they are mainstay anxiolytics/hypnotics. The analysis for BZs was also conducted. The information of "days of supply" was partially missing (30–45% by drug category) in medical claims and DPC claims between April 2011 and March 2012 because entry of the information was not mandatory in these claims before April 2012 [42]. The information of "days of supply" was not missing after April 2012. Hence, the analyses for the means of the average daily doses and the proportions of patients above clinically recommended doses were conducted for the time period after April 2012.

Furthermore, an analysis which the drug categories were subdivided into subclasses

was conducted. Sum of anxiolytics and hypnotics were classified into 3 groups (BZs, barbiturates and non-barbiturates [BARs], and others). The non-barbiturates other than BZs which are specified as addictive drugs in Japanese package inserts like barbiturates were included in BARs. Antidepressants were classified into 5 groups (tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs], and others) and antipsychotics were divided into 2 groups (typical and atypical antipsychotics). The classification of the subclasses is described in Appendix Table 1. The proportion of patients who were prescribed 2 or more drugs within the same drug subclass was calculated in each month by drug category.

In the MincaCare database, we could follow all insurance-covered prescription of patients. An analysis of prescription change in patient-level was also conducted utilizing this advantage. The proportion of patients was calculated who were prescribed 3 or more anxiolytics or 3 or more hypnotics before the introduction of the polypharmacy reduction policy (April 1st, 2012) and the number of prescribed drugs was reduced to less than 3 after the policy introduction by drug category. Similar analyses were conducted for two revisions of the policy occurred in 2014 (October 1st, 2014) and 2016 (April 1st, 2016) by drug category (Table 1). Observation period was 3 months before and after the policy introduction or revisions, respectively.

The executing rates of nonpharmacological treatments (psychotherapy; hospital-visit psychotherapy, in-hospital psychotherapy, and in-house psychotherapy, psychiatric care, CBT, psychosomatic therapy, and home-visit nursing) were also calculated in each month.

2.2.1.4 Statistical Analysis

Characteristics of patients who had any prescription records for the psychotropic drugs were summarized using descriptive statistics in each segmented period, where the definition of the segment is given below.

Segmented regression analysis of interrupted time series [43] using SAS proc autoreg (SAS/ETS software, version 9.4 of the SAS System for Microsoft Windows, SAS Institute Inc., Cary, NC, USA) was conducted to estimate the changes following the introduction or revisions of the polypharmacy reduction policy for the psychotropic drugs. This method allows one to assess how much an intervention such as policy introduction affects specific outcomes immediately and over time. Each segment of the series is allowed to exhibit both a level (intercept) and a trend (slope). A change in level, i.e., a jump or drop in the outcome after the intervention, constitutes an abrupt intervention effect. A change in trend is defined by an increase or decrease in the slope of the segment after the intervention as compared with the segment preceding the intervention. A change in trend represents a gradual change in the value of the outcome during the segment [43]. In this study, dependent variables of the segmented regression analysis were the proportions of patients in various categories (≥3 drugs, ≥4 drugs, patients above clinically recommended doses) and the means of the average daily doses by drug category. The analysis for the proportions of patients with 3 or more or 4 or more drugs were conducted for 4 drug categories (anxiolytics, hypnotics, antidepressants, and antipsychotics) and BZs. The analyses for the proportions of patients above clinically recommended doses and the means of the average daily doses were conducted for sum of anxiolytics and hypnotics, BZs, antidepressants, and antipsychotics. Independent variables were level and trend change indicator variables

for each of the segmented period.

The study period was divided into 5 segments: period 1; “Baseline” (from April 2011 to March 2012), period 2; “Introduction of the policy” (from April 2012 to March 2014), period 3; “Notification of the revision in 2014” (from April 2014 to September 2014), period 4; “Enforcement of the revision in 2014” (from October 2014 to March 2016), and period 5; “Revision in 2016” (from April 2016 to March 2017). The period 3 was considered as a “phase-in” period before the first revision because the first revision of the polypharmacy reduction policy was notified in April 2014 and enforced in October 2014. The segmented regression analysis was carried out in steps. First, stepwise autoregression with significance level of 0.05 was used to select the appropriate autocorrelation structure for the full model. Following selection of the autocorrelation structure, the full model was examined in terms of appropriateness of autocorrelation structure (generalized Durbin-Watson test) and for the degree of heteroscedasticity (Portmanteau Q test, Engle’s Lagrange multiplier test). Next, the most parsimonious model was identified by successively eliminating least significant regression terms. The significance level of 0.05 was used as the criterion for retention. The final parsimonious model was again examined for the appropriateness of autocorrelation structure and for the degree of heteroscedasticity.

In addition, observed changes of the proportions of patients by the number of prescribed drugs were described for 4 drug categories of the psychotropic drugs, sum of anxiolytics and hypnotics, BZs, and sum of psychotropic drugs (i.e., sum of anxiolytics, hypnotics, antidepressants, and antipsychotics) to capture the long-term prescription trend between April 2011 and March 2017. For patients within or above clinically recommended doses, the means of the average daily doses by the number of prescribed

drugs were described for sum of anxiolytics and hypnotics, BZs, antidepressants, and antipsychotics throughout the study period. The analysis of prescription change in patient-level including test of difference in proportion was conducted based on the method by Thomson [44] because of partial overlap of samples. The proportions of patients who were prescribed 2 or more drugs within the same drug subclass and the executing rates of nonpharmacological treatments were plotted throughout the study period.

The analyses restricted to the patients who were continuously enrolled in the database during the study period were conducted as sensitivity analyses for the observed changes of the proportions of patients by the number of prescribed drugs and those above clinically recommended doses as well as the means of the average daily doses in order to examine the robustness of the results.

Data analyses other than the segmented regression analysis were conducted using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.2.2 Results

2.2.2.1 Patient characteristics

A total of 312,167 patients had at least one prescription record for the psychotropic drugs during the study period. The patient characteristics were stable throughout the study period (Table 2).

Table 2. Patient characteristics

		Period 1 Apr 2011 - Mar 2012 (N= 105,729)	Period 2 Apr 2012 - Mar 2014 (N=152,543)	Period 3 Apr 2014 - Sep 2014 (N= 76,128)	Period 4 Oct 2014 - Mar 2016 (N=126,490)	Period 5 Apr 2016 - Mar 2017 (N=99,520)
Sex	Male (%)	46.7	46.8	47.9	47.2	47.9
	Female (%)	53.3	53.2	52.1	52.8	52.1
Age [a]	Mean (SD)	42.7 (18.2)	42.1 (18.0)	44.3 (17.1)	43.1 (17.4)	43.7 (17.1)
	< 18 years (%)	10.0	10.3	7.6	8.8	8.1
	18-24 (%)	4.6	4.8	4.3	5.1	5.1
	25-34 (%)	15.4	15.4	13.2	14.0	13.7
	35-49 (%)	32.7	33.8	35.4	34.5	34.1
	50-64 (%)	25.6	24.8	26.6	26.0	27.1
	65-74 (%)	11.7	10.9	12.8	11.5	11.8

N, total number of patients who were prescribed at least one psychotropic drug in each segmented period; SD, standard deviation.

[a] As of the initial month of prescription records for any psychotropic drugs in each segmented period.

2.2.2.2 Effect of the polypharmacy reduction policy on prescription of psychotropic drugs

The observed changes of the proportions of patients by the number of prescribed drugs are shown in Table 3. The estimated changes of the proportions of patients with "3 or more" or "4 or more" drugs following the introduction or revisions of the polypharmacy reduction policy based on the most parsimonious segmented regression model are shown in Table 4 and Figure 1.

For anxiolytics and hypnotics, the polypharmacy reduction policy was introduced in April 2012 and revised in October 2014. The revision of the policy in 2014 was notified in April 2014 (Table 1). For the proportions of patients with 3 or more anxiolytics, there were immediate and notable drops in the levels at 3 timepoints (policy introduction in April 2012, notification of the revision in April 2014, and enforcement of the revision in October 2014); there was a slight positive change in the trend (slope) at the policy introduction in April 2012 compared to the preceding period (Table 4), but the overall slope remained slightly negative throughout the study period (Figure 1(a)).

For the proportions of patients with 3 or more hypnotics, there was a drop in the level at the enforcement of the revision in October 2014; there were negative changes in the trends at 2 timepoints (policy introduction in April 2012 and notification of the revision in April 2014) followed by a positive change in the trend after the enforcement of the revision in October 2014 (Table 4), although the overall slope was consistently negative after April 2012 (Figure 1(b)). The largest negative change in the trend compared to the preceding period was observed after the notification of the revision in April 2014. The proportions of patients with "3 or more anxiolytics" and "3 or more hypnotics" dropped from 1.9% and 4.8% in April 2011 to 0.9% and 2.0% in March 2017, respectively (Table 3).

The polypharmacy reduction policy for antidepressants and antipsychotics was introduced in October 2014 after the notification in April 2014 and tightened in April 2016 (Table 1). Thus, prescription of 4 or more antidepressants and 4 or more antipsychotics were subject to the reduction criteria in 2014, and prescription of 3 or more antidepressants and 3 or more antipsychotics were subject to the criteria in 2016 (Table 1). There were drops in both the levels and trends of the proportions of patients with 3 or more antidepressants as well as antipsychotics after the policy revision in April 2016 (Table 4, Figure 1(c), (e)). There were some changes in the levels or trends of the proportions of patients with 4 or more antidepressants as well as antipsychotics between April 2014 and March 2017 (Table 4, Figure 1(d), (f)). Consistent downward trends (slopes) were seen throughout the study period, although the numerical values of the slopes varied in each segmented period for the proportions of patients with "3 or more" and "4 or more" antidepressants as well as antipsychotics (Figure 1(c)–(f)). The proportions of patients with "3 or more" and "4 or more" antidepressants dropped from

4.5% and 0.7% in April 2011 to 1.2% and 0.1% in March 2017, respectively (Table 3). The proportions of patients with “3 or more” and “4 or more” antipsychotics dropped from 4.9% and 1.1% in April 2011 to 2.4% and 0.5% in March 2017, respectively (Table 3).

For BZs, which are mainstay anxiolytics/hypnotics, the proportion of patients with 3 or more BZs had a downward trend before the introduction of the policy in April 2012, but the continuous downward trend was not seen after April 2012 (Table 4, Figure 1(g)). In addition, there were no significant drops in the levels of the proportions of patients with 3 or more BZs after the policy introduction in April 2012 as well as after the notification and enforcement of the revision in 2014. The proportion of patients with 3 or more BZs was still 8.9% in March 2017 (Table 3).

The proportions of patients with 2 drugs were unchanged or increased in all drug categories throughout the study period (Table 3), which contrasted with the proportions of patients with 3 or more drugs which dropped after the introduction or revisions of the polypharmacy reduction policy. The proportions of patients with monotherapy were increased from April 2011 to March 2017 only for antidepressants (76.9%→80.8%) and antipsychotics (79.8%→82.1%), and not changed or decreased for anxiolytics (85.2%→85.7%), hypnotics (78.6%→77.6%), sum of anxiolytics and hypnotics (68.1%→65.7%), BZs (68.0%→67.3%), and sum of psychotropic drugs (52.1%→49.9%).

The estimated changes of the proportions of patients above clinically recommended doses and the means of the average daily doses after April 2012 based on the most parsimonious segmented regression model are shown in Table 5, Figure 2, and Figure 3.

The polypharmacy reduction policy for anxiolytics and hypnotics was introduced in April 2012 and tightened in October 2014, and that for antidepressants and

antipsychotics was introduced in October 2014 and tightened in April 2016. The revision of the policy in 2014 was notified in April 2014 (Table 1). For sum of anxiolytics and hypnotics, BZs, antidepressants, and antipsychotics, the proportions of patients above clinically recommended doses had downward trends before the notification of the revision in April 2014, but the continuous downward trends were not seen after April 2014 (Table 5, Figure 2(a)–(d)). There were some ups and downs in sum of anxiolytics and hypnotics, BZs, and antidepressants, but there were no statistically significant drops in the levels or downward changes in the trends after the strictest revisions of the policy, that is after the notification and enforcement of the revision in 2014 for anxiolytics and hypnotics, and after the revision in 2016 for antidepressants (Table 5, Figure 2(a)–(c)). In addition, the proportions of patients above clinically recommended doses were increased or not changed between March 2014 (before the notification of the revision in 2014) and March 2017 for sum of anxiolytics and hypnotics, BZs, and antidepressants (Figure 2(a)–(c)). On the other hand, for antipsychotics, there was a statistically significant downward change in the trend after the strictest policy revision in April 2016, and the proportion of patients above clinically recommended doses was decreased after April 2016 (Table 5, Figure 2(d)).

The means of average daily doses generally showed similar tendency to the proportions of patients above clinically recommended doses except the significant drops after the enforcement of the revision in October 2014 for sum of anxiolytics and hypnotics as well as BZs (Table 5, Figure 3). As a whole, the means of the average daily doses were not decreased between March 2014 (before the notification of the revision in 2014) and March 2017 for antidepressants (Figure 3(c)). On the other hand, the means of the average daily doses were decreased after the revision in April 2016 for

sum of anxiolytics and hypnotics, BZs, and antipsychotics (Figure 3(a), (b), (d)).

The analysis based on the full segmented regression model generally yielded similar results (Appendix Tables 2 and 3). In addition, the results of the sensitivity analysis restricted to the patients who were continuously enrolled in the database during the study period supported the robustness of these results (data not shown).

The results of the analysis in patient-level showed that the proportions of patients who were reduced the number of prescribed psychotropic drugs from 3 or more to less than 3 were significantly increased after the enforcement of the revision in October 2014 for anxiolytics and hypnotics), and after the revision in April 2016 for antidepressants and antipsychotics (data not shown).

The proportions of patients who were prescribed 2 or more drugs within the same drug subclass were plotted in Figure 4. The proportions of patients who were prescribed 2 or more drugs within the same drug subclass in the patients who were prescribed 2 or more drugs were 89.6%–94.4%, 10.3–16.9%, and 61.5–68.4% in sum of anxiolytics and hypnotics, antidepressants, and antipsychotics, respectively. The proportion of patients who were prescribed 2 or more drugs within the same drug subclass was decreased only in antidepressants.

Table 3. Observed changes of psychotropic prescriptions by the number of prescribed drugs

	Apr 2011	Oct 2011	Apr 2012	Oct 2012	Apr 2013	Oct 2013	Apr 2014	Oct 2014	Apr 2015	Oct 2015	Apr 2016	Oct 2016	Mar 2017
Anxiolytics (N)	22032	21928	20359	20898	20201	20565	21098	21755	21357	22324	21102	21141	20542
1	85.2	85.6	86.6	86.7	87.0	86.5	86.1	85.8	85.9	85.6	85.8	85.5	85.7
2	12.9	12.6	11.7	11.8	11.6	12.0	12.6	13.2	13.2	13.5	13.3	13.5	13.4
≥3	1.9	1.8	1.6	1.5	1.4	1.5	1.3	1.0	0.9	0.9	1.0	0.9	0.9
Hypnotics (N)	18159	18815	18160	18987	18521	18836	18914	19775	19427	20391	19416	19916	19859
1	78.6	78.3	78.8	79.1	79.1	78.9	77.5	78.4	77.8	77.8	77.4	77.2	77.6
2	16.7	16.8	16.4	16.3	16.3	16.6	18.2	19.0	19.9	20.0	20.4	20.8	20.4
≥3	4.8	4.8	4.8	4.7	4.6	4.5	4.3	2.6	2.3	2.2	2.2	2.0	2.0
Antidepressants (N)	14670	14936	14767	14898	14594	14351	14486	14895	14853	15109	14657	15035	14941
1	76.9	77.2	77.4	78.5	79.2	79.5	80.0	78.9	79.1	79.5	79.6	81.0	80.8
2	18.6	18.4	18.7	17.9	17.3	17.1	17.0	17.9	17.9	17.5	18.4	17.7	18.1
≥3	4.5	4.4	4.0	3.6	3.4	3.4	3.0	3.1	3.0	3.1	2.0	1.3	1.2
≥4	0.7	0.8	0.7	0.6	0.5	0.6	0.5	0.3	0.3	0.3	0.3	0.1	0.1
Antipsychotics (N)	8522	8734	8686	8779	9113	9169	9401	9639	9490	9818	9572	9699	9675
1	79.8	80.4	80.0	79.8	80.8	80.4	80.9	81.5	80.3	80.7	81.2	81.5	82.1
2	15.3	14.7	14.9	15.2	14.3	14.9	14.3	14.0	15.2	15.2	15.2	15.7	15.5
≥3	4.9	5.0	5.1	4.9	4.9	4.7	4.8	4.4	4.5	4.1	3.6	2.9	2.4
≥4	1.1	1.3	1.1	1.2	1.2	1.2	1.0	0.9	0.8	0.7	0.6	0.4	0.5
Sum of anxiolytics and hypnotics (N)	33150	33674	32054	33313	32278	32636	32853	33972	33239	34688	32871	33324	32891
1	68.1	68.2	69.1	69.5	69.3	68.4	67.1	66.8	66.2	65.9	65.5	65.4	65.7
2	21.3	21.2	21.1	20.9	21.3	21.9	22.4	23.2	23.8	23.7	24.2	24.3	24.2
≥3	10.6	10.6	9.8	9.6	9.4	9.8	10.6	10.0	10.1	10.4	10.3	10.3	10.1
BZs (N)	30968	31513	29937	31132	30137	30728	30875	32005	31208	32586	30898	31183	30635
1	68.0	68.2	69.3	69.8	69.7	69.0	67.4	67.1	66.9	66.7	66.8	66.6	67.3
2	21.8	21.8	21.4	21.1	21.5	21.9	22.7	23.5	23.9	23.8	24.0	24.2	23.8
≥3	10.2	10.0	9.3	9.0	8.8	9.2	9.9	9.4	9.2	9.5	9.2	9.2	8.9
Sum of psychotropic drugs (N)	39189	39849	38603	40039	39030	38922	38957	40134	39372	40842	38922	39630	39335
1	52.1	52.2	52.5	53.2	52.7	52.0	50.7	50.4	50.0	50.0	49.4	49.4	49.9
2	22.1	22.1	22.2	22.5	22.7	22.7	23.0	23.2	23.3	23.2	23.6	24.0	23.8
3	12.0	12.0	12.2	12.0	12.3	12.5	12.9	13.0	13.2	13.3	13.5	13.4	13.4
4	6.7	6.9	6.7	6.4	6.3	6.5	7.0	7.1	7.2	7.3	7.2	7.2	7.2
5	3.7	3.6	3.3	3.2	3.2	3.5	3.4	3.7	3.6	3.5	3.5	3.7	3.4
≥6	3.3	3.2	3.1	2.8	2.8	2.8	2.9	2.6	2.8	2.7	2.7	2.3	2.3

BZ, benzodiazepine receptor agonist; N, total number of patients who were prescribed at least one drug within the drug category in each month; sum of psychotropic drugs, sum of anxiolytics, hypnotics, antidepressants, and antipsychotics.

Values displayed are proportions of patients (%). Total number of patients who were prescribed at least one drug within the drug category in each month was used as a denominator.

Table 4. Estimated changes of the proportions of patients with 3 or more or 4 or more drugs based on the most parsimonious segmented regression model

Parameter	Period 1 (Baseline)		Period 2 (Introduction of the policy)		Period 3 (Notification of the revision in 2014)		Period 4 (Enforcement of the revision in 2014)		Period 5 (Revision in 2016)	
	Apr 2011 - Mar 2012		Apr 2012 - Mar 2014		Apr 2014 - Sep 2014		Oct 2014 - Mar 2016		Apr 2016 - Mar 2017	
	Intercept	Baseline trend	Level change	Trend change	Level change	Trend change	Level change	Trend change	Level change	Trend change
Anxiolytics (≥3) (%)	1.8966 (0.0406)	-0.2304 (0.0738)	-0.1411 (0.0496)	0.1884 (0.0758)	-0.1433 (0.0394)		-0.2979 (0.0406)			
Hypnotics (≥3) (%)	4.8287 (0.0431)			-0.1824 (0.0427)		-3.2988 (0.3204)	-0.2541 (0.1250)	3.2556 (0.3072)		
Antidepressants (≥3) (%)	4.5176 (0.0302)	-0.4524 (0.0263)	-0.1601 (0.0563)			0.2868 (0.0617)	0.2062 (0.0694)		-1.1167 (0.0742)	-0.6192 (0.1134)
Antidepressants (≥4) (%)	0.6843 (0.0135)		-0.0778 (0.0215)	-0.0608 (0.0145)		-0.2316 (0.0622)		0.2256 (0.0665)		-0.1416 (0.0499)
Antipsychotics (≥3) (%)	4.9358 (0.0414)		0.1415 (0.0689)	-0.2244 (0.0500)	0.2214 (0.1026)	-0.6156 (0.2388)		0.6984 (0.2772)	-0.8185 (0.0998)	-1.0812 (0.1584)
Antipsychotics (≥4) (%)	1.1380 (0.0138)				-0.1147 (0.0360)		-0.1234 (0.0454)	-0.1344 (0.0363)	-0.1524 (0.0532)	
BZs (≥3) (%)	10.2709 (0.2657)	-1.0200 (0.3252)		1.0056 (0.3600)						

BZ, benzodiazepine receptor agonist.

The most parsimonious model was derived from the full model by successively eliminating the least significant term with $p > 0.05$. Only those terms significant at significance level 0.05 at the final iteration are displayed. Time unit of trend is per year. Values displayed are point estimates (standard errors) of each parameter. The level change parameter and its statistical significance corresponds to the jump between the end of the preceding period and the start of the current period. The trend change parameter and its statistical significance corresponds to the change in trend from the preceding period to the current period. Actual value of the slope in each period is computed by sum of the baseline trend and the cumulative sum of the trends in the previous periods. The periods when the relevant reduction criteria of the polypharmacy reduction policy were introduced or revised are displayed in the gray cells.

Table 5. Estimated changes of the proportions of patients above clinically recommended doses and the means of the average daily doses based on the most parsimonious segmented regression model

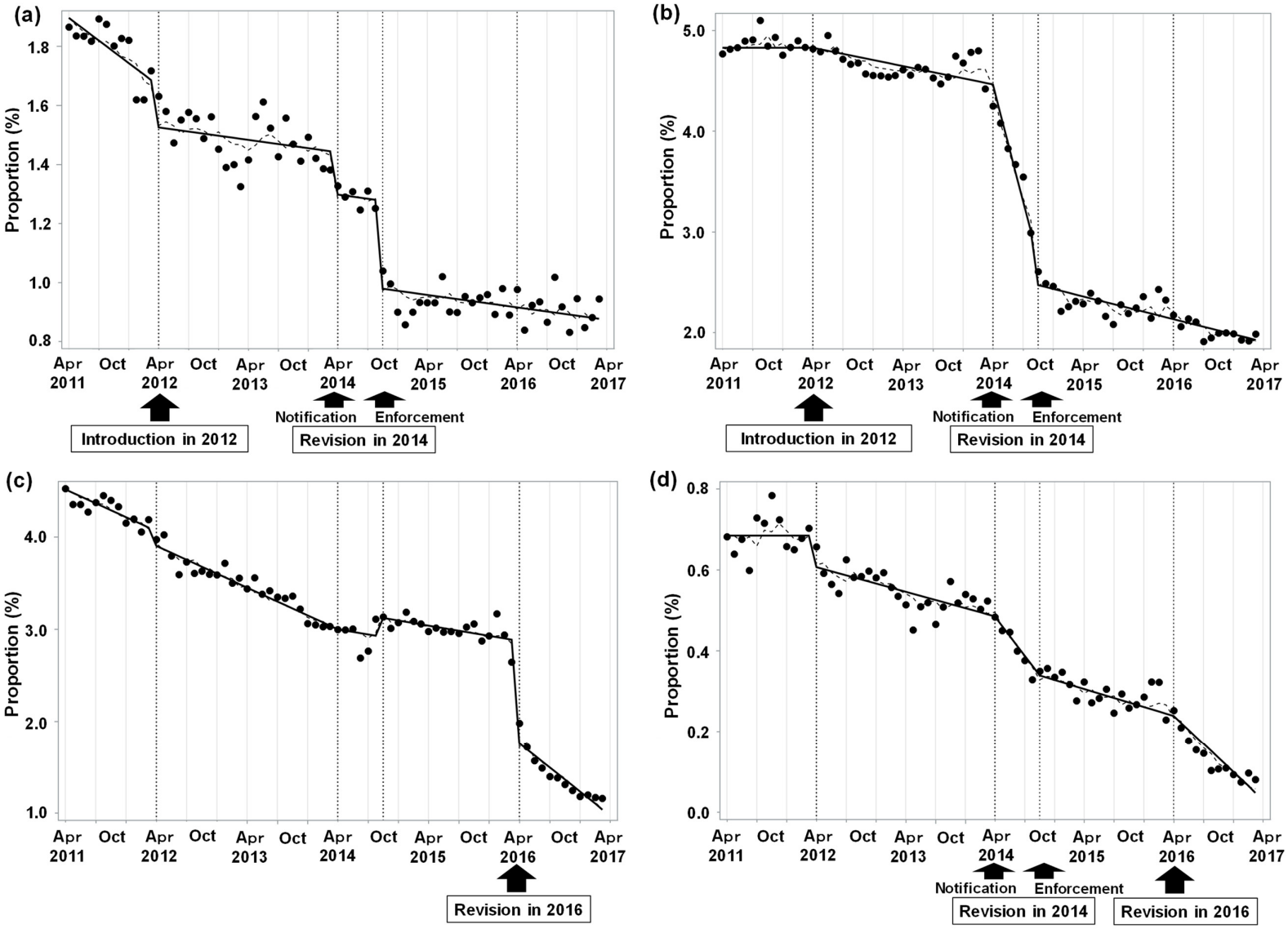
Parameter	Period 2 (Introduction of the policy) Apr 2012 - Mar 2014		Period 3 (Notification of the revision in 2014) Apr 2014 - Sep 2014		Period 4 (Enforcement of the revision in 2014) Oct 2014 - Mar 2016		Period 5 (Revision in 2016) Apr 2016 - Mar 2017	
	Intercept	Baseline trend	Level change	Trend change	Level change	Trend change	Level change	Trend change
Proportion of patients above clinically recommended doses								
Sum of anxiolytics and hypnotics > 15 mg/day (%) [a]	19.6607 (0.1411)	-0.5160 (0.0691)	0.5013 (0.1104)	0.6288 (0.0905)				-0.8028 (0.1848)
BZs > 15 mg/day (%) [a]	18.5358 (0.1568)	-0.3672 (0.0766)	0.6110 (0.1328)			0.6756 (0.1172)		-0.7620 (0.2244)
Antidepressants > 200 mg/day (%) [a]	12.4249 (0.0531)	-0.0459 (0.0206)				-0.1440 (0.0494)		0.7752 (0.1284)
Antipsychotics > 450 mg/day (%) [a]	13.4086 (0.1775)	-0.9420 (0.0862)	0.4037 (0.1477)			1.0368 (0.1344)		-0.9936 (0.2580)
Mean of average daily doses								
Sum of anxiolytics and hypnotics (mg/day) [b]	14.8746 (0.1159)	-0.4056 (0.0567)	0.2834 (0.1018)		-0.2284 (0.0963)	0.5580 (0.0913)		-0.7440 (0.1776)
BZs (mg/day) [b]	14.4497 (0.1156)	-0.3708 (0.0565)	0.2773 (0.1014)		-0.2065 (0.0959)	0.5808 (0.0912)		-0.5316 (0.1776)
Antidepressants (mg/day) [b]	109.1584 (0.3876)	1.0476 (0.1404)		-1.6992 (0.2160)				1.5852 (0.3840)
Antipsychotics (mg/day) [b]	229.2387 (2.5214)	-7.9116 (0.9972)				8.9544 (2.3940)		-16.2432 (4.8996)

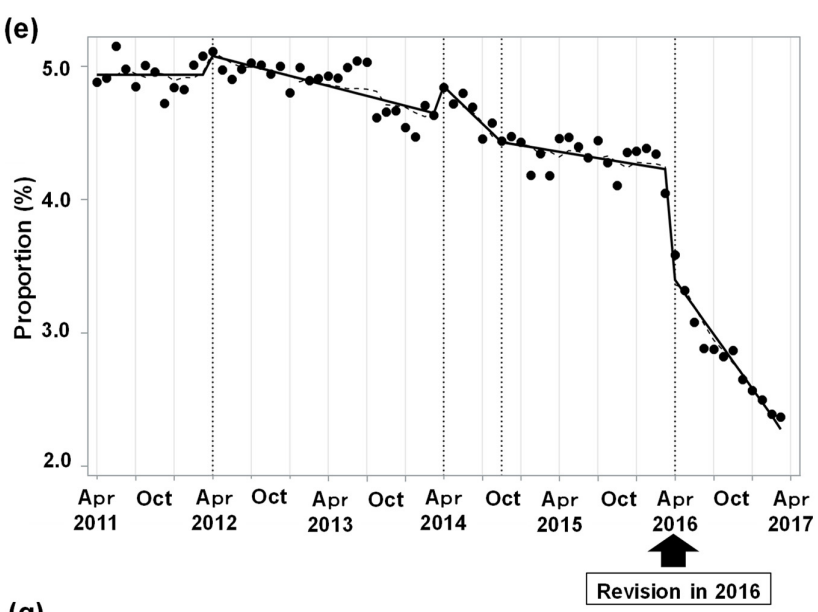
BZ, benzodiazepine receptor agonist.

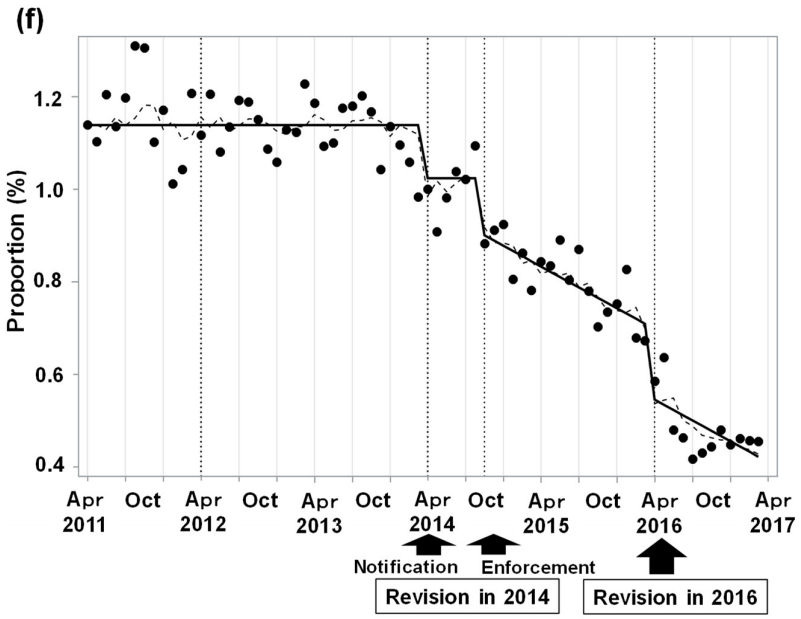
The most parsimonious model was derived from the full model by successively eliminating the least significant term with $p > 0.05$. Only those terms significant at significance level 0.05 at the final iteration are displayed. Time unit of trend is per year. Diazepam-equivalent doses for anxiolytics and hypnotics as well as BZs, imipramine-equivalent doses for antidepressants, and chlorpromazine-equivalent doses for antipsychotics were used. The level change parameter and its statistical significance corresponds to the jump between the end of the preceding period and the start of the current period. The trend change parameter and its statistical significance corresponds to the change in trend from the preceding period to the current period. Actual value of the slope in each period is computed by sum of the baseline trend and the cumulative sum of the trends in the previous periods.

[a] Proportion of patients prescribed with more than clinically recommended doses in Japan. Values displayed are point estimates (standard errors) of each parameter.

[b] Mean of the average daily doses. Values displayed are point estimates (standard errors) of each parameter.


(a)
Proportion (%)
1.8
1.6
1.4
1.2
1.0
0.8
Apr 2011
Oct
Apr 2012
Oct
Apr 2013
Oct
Apr 2014
Oct
Apr 2015
Oct
Apr 2016
Oct
Apr 2017
Introduction in 2012
Notification
Enforcement
Revision in 2014
(b)
Proportion (%)
5.0
4.0
3.0
2.0
Introduction in 2012
Notification
Enforcement
Revision in 2014
(c)
Proportion (%)
4.0
3.0
2.0
1.0
Revision in 2016
(d)
Proportion (%)
0.8
0.6
0.4
0.2
0.0
Notification
Enforcement
Revision in 2014
Revision in 2016





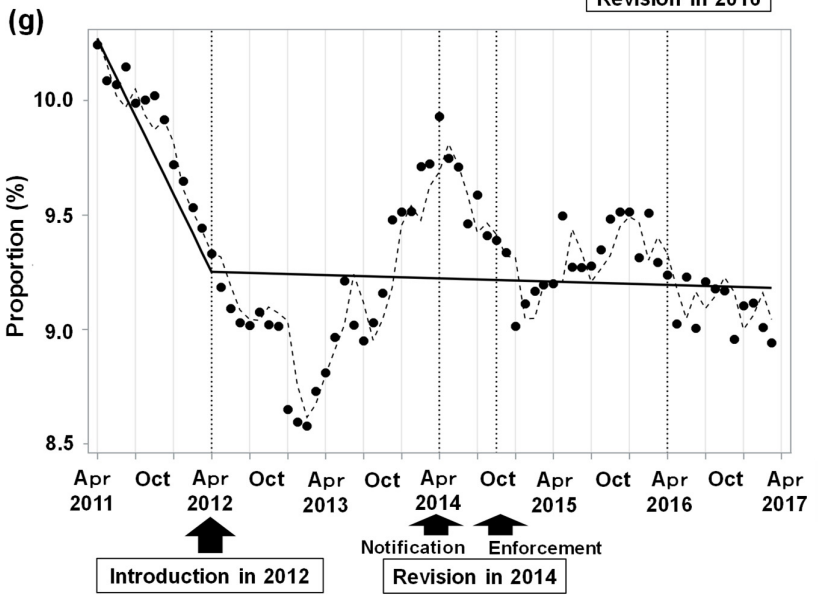


Figure 1. Estimated changes of the proportions of patients with 3 or more/ 4 or more drugs by drug category based on the most parsimonious segmented regression model: (a) anxiolytics (≥3), (b) hypnotics (≥3), (c) antidepressants (≥3), (d) antidepressants (≥4), (e) antipsychotics (≥3), (f) antipsychotics (≥4), and (g) BZs (≥3). Black circle, observed; solid line, estimated piecewise linear trend; dotted line, predicted curve based on autoregressive model. BZ, benzodiazepine receptor agonist.

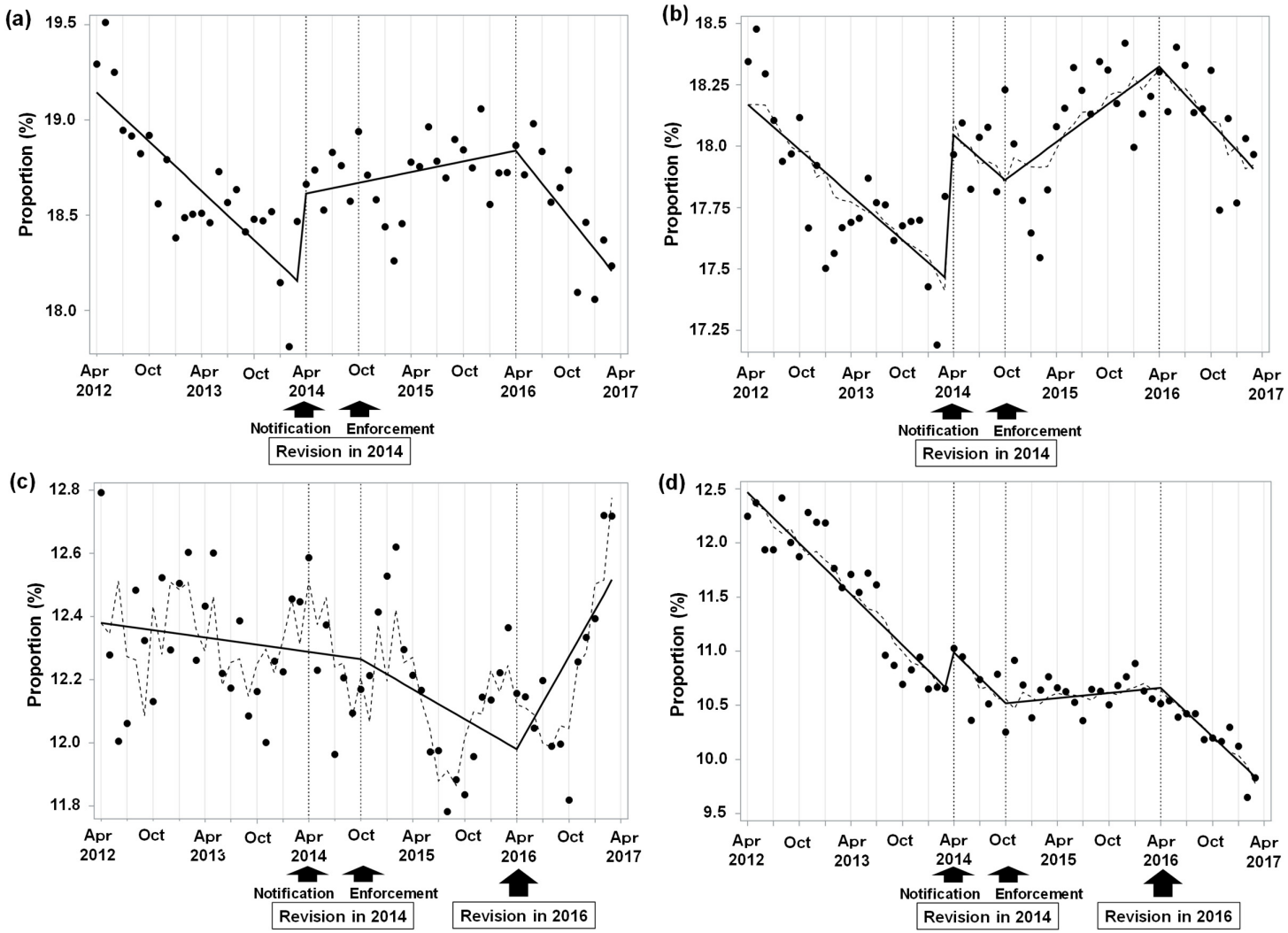


Figure 2. Estimated changes of the proportions of patients above clinically recommended doses based on the most parsimonious segmented regression model: (a) sum of anxiolytics and hypnotics, (b) BZs, (c) antidepressants, and (d) antipsychotics. Black circle, observed; solid line, estimated piecewise linear trend; dotted line, predicted curve based on autoregressive model. BZ, benzodiazepine receptor agonist.

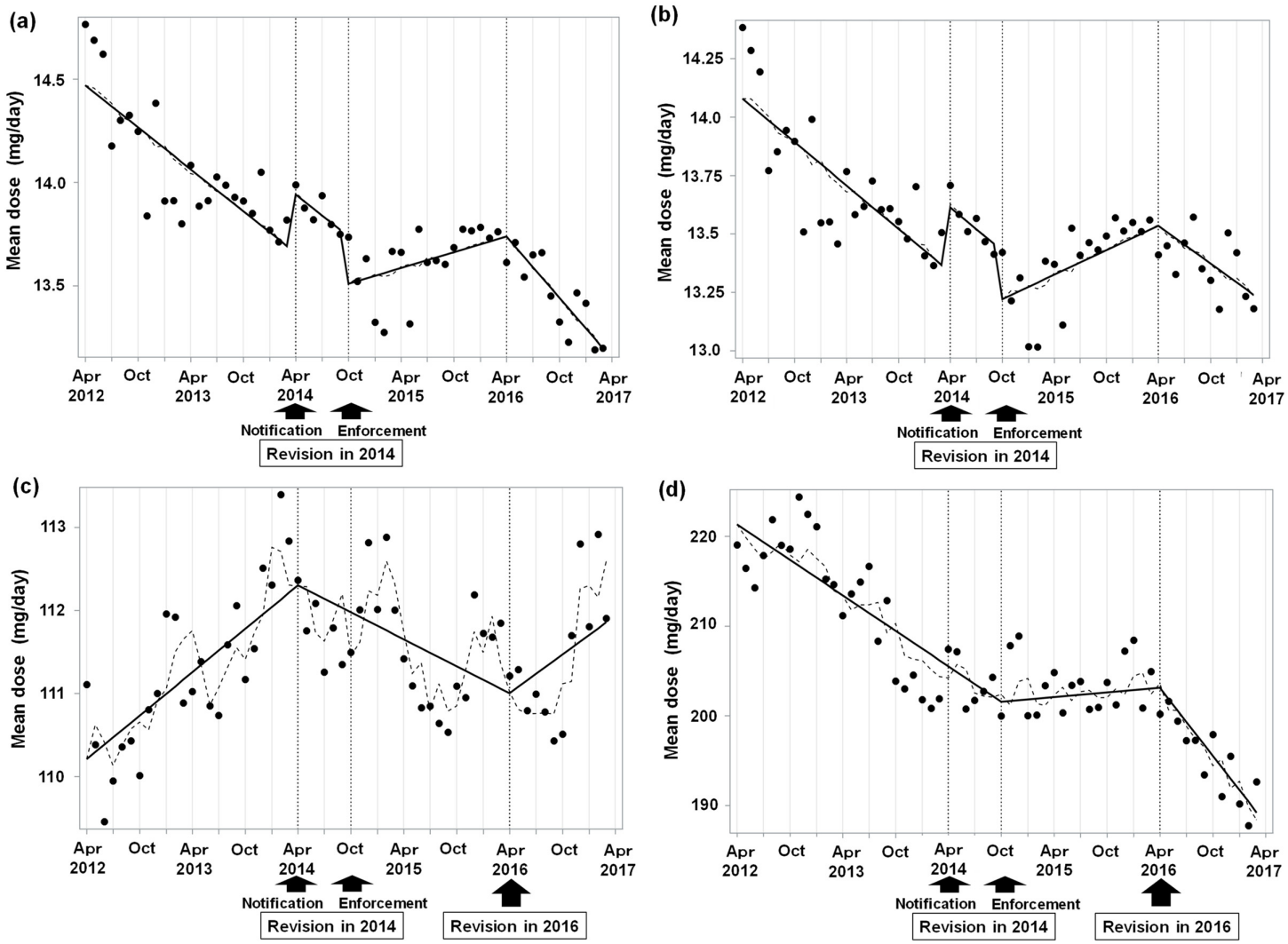


Figure 3. Estimated changes of the means of the average daily doses based on the most parsimonious segmented regression model: (a) sum of anxiolytics and hypnotics, (b) BZs, (c) antidepressants, and (d) antipsychotics. Black circle, observed; solid line, estimated piecewise linear trend; dotted line, predicted curve based on autoregressive model. BZ benzodiazepine receptor agonist.

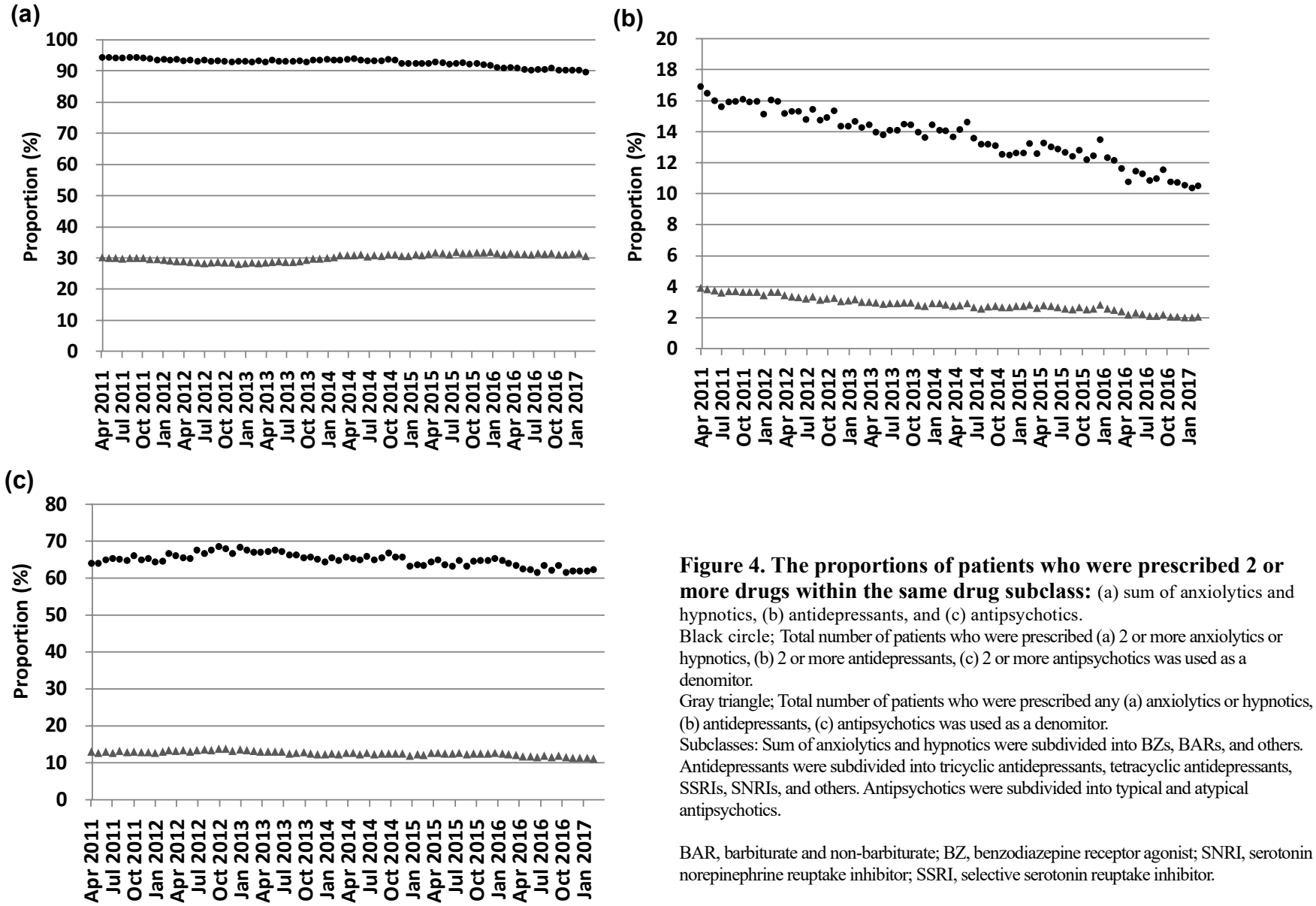


Figure 4. The proportions of patients who were prescribed 2 or more drugs within the same drug subclass: (a) sum of anxiolytics and hypnotics, (b) antidepressants, and (c) antipsychotics.
Black circle; Total number of patients who were prescribed (a) 2 or more anxiolytics or hypnotics, (b) 2 or more antidepressants, (c) 2 or more antipsychotics was used as a denomitor.
Gray triangle; Total number of patients who were prescribed any (a) anxiolytics or hypnotics, (b) antidepressants, (c) antipsychotics was used as a denomitor.
Subclasses: Sum of anxiolytics and hypnotics were subdivided into BZs, BARs, and others. Antidepressants were subdivided into tricyclic antidepressants, tetracyclic antidepressants, SSRIs, SNRIs, and others. Antipsychotics were subdivided into typical and atypical antipsychotics.

BAR, barbiturate and non-barbiturate; BZ, benzodiazepine receptor agonist; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

2.2.2.3 Doses by the number of prescribed drugs

The means of the average daily doses by the number of prescribed drugs for patients within or above clinically recommended doses are shown in Table 6. The proportion of patients with monotherapy and within clinically recommended doses was the highest (60–79%) in each drug category. On the other hand, not a few patients (7–12%) were prescribed more than clinically recommended doses even with monotherapy or 2 drugs, and sums of their proportions were not changed for sum of anxiolytics and hypnotics, BZs, and antipsychotics, and a little increased for antidepressants throughout the study period. Moreover, for sum of anxiolytics and hypnotics as well as BZs, 5–6% patients were prescribed more than 50 mg/day (diazepam-equivalent dose) despite monotherapy.

Table 6. Means of the average daily doses by the number of prescribed drugs for patients within or above clinically recommended doses

		Within clinically recommended doses							Above clinically recommended doses					
		Number of drugs	1		2		≥3		1		2		≥3	
		N	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)
Sum of anxiolytics and hypnotics	Apr 2012	28227	62.1	4.9	16.3	9.6	2.3	12.3	5.9	52.9	5.9	49.8	7.5	51.1
	Oct 2012	29156	62.7	4.8	16.1	9.5	2.3	12.2	6.0	51.4	5.7	48.6	7.3	49.7
	Apr 2013	28072	62.6	4.8	16.7	9.5	2.2	12.4	5.7	49.8	5.6	46.7	7.2	52.3
	Oct 2013	28742	62.2	4.7	17.1	9.5	2.3	12.3	5.5	51.7	5.5	45.0	7.4	50.4
	Apr 2014	28848	60.9	4.7	17.8	9.5	2.5	12.3	5.2	51.6	5.6	45.7	7.9	49.1
	Oct 2014	30054	60.5	4.7	18.0	9.5	2.5	12.1	5.2	51.2	6.2	43.2	7.5	46.7
	Apr 2015	29029	60.3	4.7	18.4	9.5	2.5	12.1	5.3	51.9	6.2	43.5	7.4	45.7
	Oct 2015	30154	60.1	4.7	18.4	9.4	2.6	12.2	5.2	50.4	6.2	46.3	7.5	44.6
	Apr 2016	28516	60.2	4.7	18.4	9.4	2.5	12.2	5.3	50.7	6.3	44.9	7.3	44.3
	Oct 2016	28564	60.0	4.7	18.8	9.4	2.5	12.1	5.3	49.6	6.2	43.6	7.2	43.2
	Mar 2017	27894	60.8	4.7	18.4	9.5	2.5	12.1	5.2	50.6	6.2	45.1	6.8	41.6
BZs	Apr 2012	28291	62.8	4.9	16.5	9.6	2.3	12.3	5.4	55.7	5.7	50.4	7.2	49.2
	Oct 2012	29315	63.2	4.8	16.4	9.5	2.3	12.2	5.6	53.3	5.5	49.1	7.0	47.7
	Apr 2013	28304	63.3	4.8	16.9	9.5	2.2	12.4	5.3	52.1	5.5	47.7	6.9	50.4
	Oct 2013	29040	62.8	4.7	17.2	9.5	2.3	12.3	5.1	54.3	5.5	45.4	7.1	48.1
	Apr 2014	29193	61.4	4.7	18.0	9.5	2.6	12.3	4.8	53.9	5.5	46.3	7.7	47.5
	Oct 2014	30362	61.1	4.7	18.1	9.5	2.5	12.1	4.9	53.0	6.2	43.6	7.1	45.0
	Apr 2015	29580	60.8	4.7	18.6	9.5	2.5	12.1	4.9	53.6	6.2	43.8	7.0	44.2
	Oct 2015	30825	60.5	4.7	18.6	9.4	2.6	12.2	4.9	52.0	6.1	45.9	7.2	44.2
	Apr 2016	29352	60.7	4.7	18.6	9.4	2.5	12.2	5.0	52.0	6.3	45.1	7.0	43.7
	Oct 2016	29575	60.3	4.7	18.9	9.4	2.4	12.1	5.0	52.0	6.3	43.8	7.1	43.3
	Mar 2017	29082	61.1	4.7	18.5	9.5	2.4	12.1	4.9	52.0	6.3	44.9	6.8	42.2

		Within clinically recommended doses							Above clinically recommended doses					
		Number of drugs	1		2		≥3		1		2		≥3	
		N	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)	%	Mean (mg/day)
Antidepressants	Apr 2012	14665	74.8	73.8	11.5	124.2	0.9	149.1	2.9	281.3	7.0	301.7	2.9	379.5
	Oct 2012	14798	75.9	74.3	11.1	123.3	0.9	150.2	2.9	290.3	6.7	306.6	2.5	379.6
	Apr 2013	14494	76.6	75.6	10.2	123.6	0.8	144.3	3.0	280.1	7.0	309.4	2.4	383.3
	Oct 2013	14241	77.0	75.9	10.0	122.5	0.9	147.0	2.8	282.1	7.0	315.5	2.4	392.6
	Apr 2014	14365	77.2	76.7	9.6	124.4	0.7	143.4	3.2	284.6	7.3	315.3	2.1	390.1
	Oct 2014	14767	76.2	75.9	10.8	125.3	0.9	149.5	3.1	282.1	7.0	317.0	2.1	383.4
	Apr 2015	14746	76.2	75.9	10.8	122.8	0.8	141.9	3.2	283.8	6.9	319.7	2.1	380.6
	Oct 2015	14997	76.6	76.1	10.9	122.0	0.7	146.4	3.1	286.3	6.6	314.8	2.2	412.9
	Apr 2016	14561	76.2	76.6	11.2	123.2	0.5	149.2	3.6	282.7	7.1	317.0	1.4	394.1
	Oct 2016	14926	77.6	77.8	10.2	123.9	0.3	146.0	3.6	279.6	7.4	322.3	0.9	369.2
	Mar 2017	14846	77.0	78.1	9.9	122.5	0.3	146.0	3.9	277.6	8.0	316.8	0.8	367.7
Antipsychotics	Apr 2012	8681	76.7	100.4	9.7	211.5	1.4	254.9	3.3	711.2	5.3	916.2	3.7	1253.8
	Oct 2012	8776	76.8	99.9	9.9	213.2	1.4	283.3	3.0	780.3	5.3	890.3	3.6	1293.4
	Apr 2013	9105	77.7	98.0	9.2	206.2	1.4	288.4	3.1	750.2	5.1	892.1	3.5	1233.0
	Oct 2013	9163	77.8	95.1	10.2	203.4	1.3	264.1	2.7	754.8	4.7	893.0	3.4	1305.7
	Apr 2014	9395	78.1	96.6	9.6	203.7	1.3	286.1	2.8	760.6	4.6	850.9	3.5	1343.9
	Oct 2014	9637	79.1	96.5	9.4	207.8	1.3	275.9	2.5	756.6	4.7	880.6	3.1	1307.3
	Apr 2015	9483	77.6	96.7	10.4	202.2	1.3	274.8	2.7	800.8	4.8	943.9	3.1	1213.3
	Oct 2015	9815	78.1	94.5	10.2	205.4	1.2	273.7	2.6	796.5	4.9	964.9	2.9	1264.6
	Apr 2016	9566	78.4	96.7	10.0	207.8	1.1	275.3	2.8	774.2	5.2	884.8	2.5	1314.3
	Oct 2016	9698	78.6	95.0	10.4	208.3	0.9	289.2	2.9	845.8	5.3	903.7	2.0	1334.0
	Mar 2017	9674	79.2	94.6	10.3	205.6	0.6	280.8	2.9	795.2	5.2	910.0	1.7	1406.8

BZ, benzodiazepine receptor agonist.

Total of 15 mg/day (diazepam-equivalent dose) for sum of anxiolytics and hypnotics as well as BZs, 200 mg/day (imipramine-equivalent dose) for antidepressants, and 450 mg/day (chlorpromazine-equivalent dose) for antipsychotics were defined as the upper limits of the clinically recommended doses based on the reference drugs' Japanese package inserts.

2.2.2.4 Nonpharmacological treatments

The executing rates of nonpharmacological treatments were plotted in Figure 5. The proportion of patients with any nonpharmacological treatments was under 2.0% and there was no tendency to increase after the revisions of the polypharmacy reduction policy. The executing rate of the hospital-visit psychotherapy was highest in the nonpharmacological treatments, but that was only 1.2–1.8%. The executing rates of other nonpharmacological treatments were under 0.13%. The proportion of patients with psychotropic prescriptions in the study population was 16.6–28.9% in each month, and the proportion of patients with nonpharmacological treatments was much lower than that with psychotropic prescriptions.

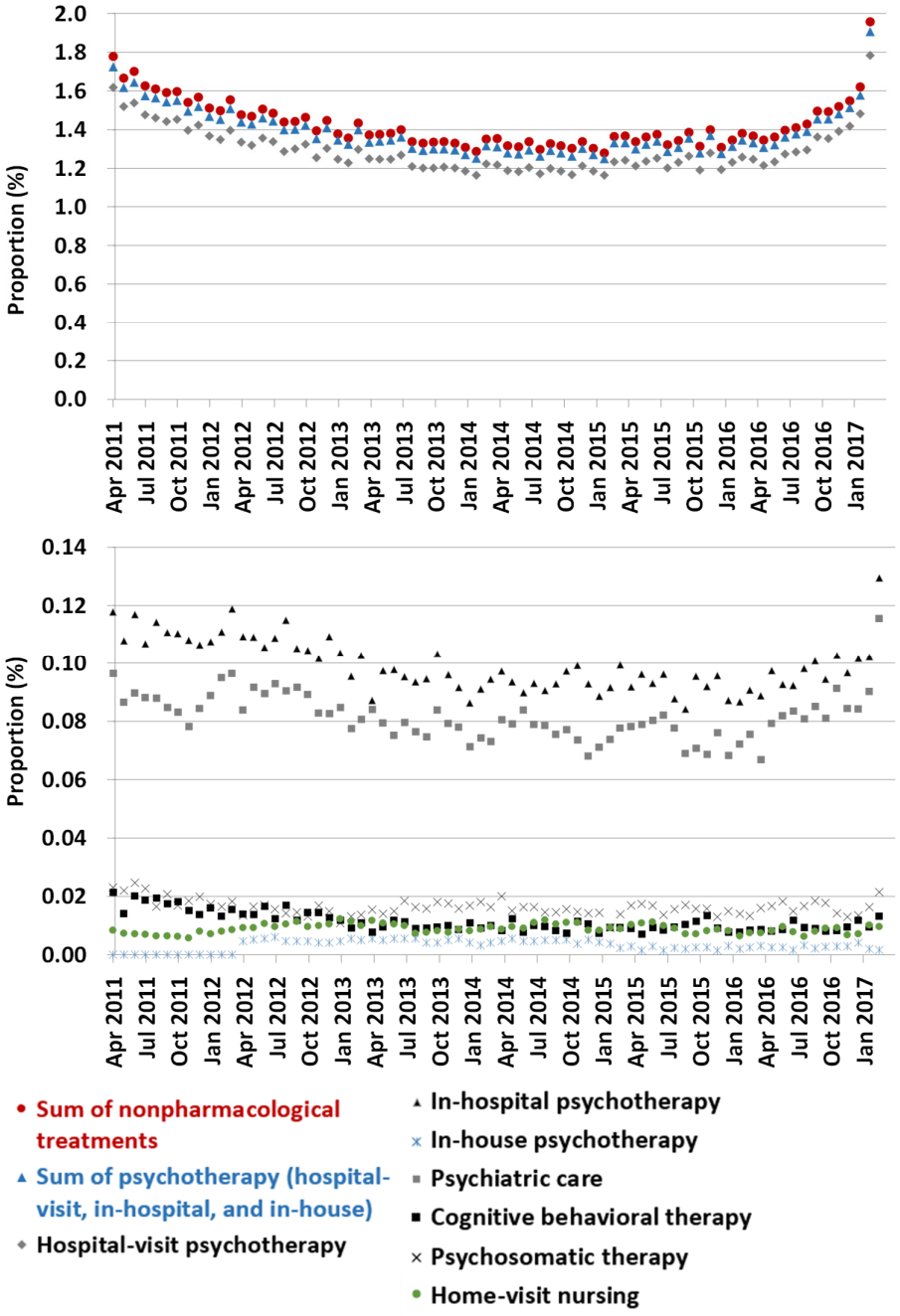


Figure 5. Executing rates of nonpharmacological treatments

The proportion of the sum of nonpharmacological treatments was defined as the proportion of patients with any nonpharmacological treatments (psychotherapy; hospital-visit psychotherapy, in-hospital psychotherapy, and in-house psychotherapy, psychiatric care, CBT, psychosomatic therapy, or home-visit nursing). The proportion of the sum of psychotherapy was defined as the proportion of patients with any psychotherapy (hospital-visit psychotherapy, in-hospital psychotherapy, or in-house psychotherapy). Total number of patients who were in the database in each month among the study population was used as a denominator. CBT, cognitive behavioral therapy.

2.3 Research 1-2 Investigation into trends in prescription of psychotropic drugs in DPC hospitals based on the MDV database

2.3.1 Methods

2.3.1.1 Data Source

Research 1-2 was conducted using the MDV database which included both outpatients' and inpatients' data provided by hospitals which use the DPC/PDPS [21]. As of March 2017, the database covers around 17.9 million accumulated patients of all ages from 291 hospitals throughout Japan capable of treating advanced stage patients, including, but not limited to, acute care facilities. The MDV database contains anonymized patient identifiers, as well as patient sex, birth years, departments visited, dates of medical services, diagnosis codes, hospitalization, medical procedures and test orders, operations, and prescribed medications. In this study, data between April 2011 and March 2017 were used.

2.3.1.2 Study Population

Patients who were prescribed at least one psychotropic drug (anxiolytic, hypnotic, antidepressant, or antipsychotic) between April 2011 and March 2017 (study period) were defined as a study population. The classification of the psychotropic drugs was based on the Japanese polypharmacy reduction policy revised in 2016 (Appendix Table 1) [33].

2.3.1.3 Outcome Measures

The monthly utilizations of the psychotropic drugs were measured as total number of prescribed drugs in each month by drug category. In addition, average daily dose of the psychotropic drugs was calculated for each patient in each month by drug category

and the mean of the average daily doses as well as the proportion of patients who were prescribed more than clinically recommended doses in Japan were calculated in the procedure described in Section 2.2.1.3.

2.3.1.4 Statistical Analysis

Characteristics of patients who had any prescription records for the psychotropic drugs were summarized using descriptive statistics in each segmented period, where the definition of the segment is in Section 2.2.1.4. Observed changes of the proportions of patients by the number of prescribed drugs were described and plotted for 4 drug categories of the psychotropic drugs, sum of anxiolytics and hypnotics, BZs, and sum of psychotropic drugs (i.e., sum of anxiolytics, hypnotics, antidepressants, and antipsychotics). Observed changes of the proportions of patients above clinically recommended doses and the means of the average daily doses were plotted for sum of anxiolytics and hypnotics, BZs, antidepressants, and antipsychotics. These analyses were performed for the following patient groups; (a) outpatients aged <65 years, (b) inpatients aged < 65 years, (c) outpatients aged ≥ 65 years, and (d) inpatients aged ≥ 65 years. Any statistical tests were not performed. In the DPC data entry rule, entry of the information of medications which inpatients bring themselves became mandatory in October 2016 [45], which would make it difficult to compare the prescription trends before October 2016 and after then. Hence, for the inpatients, the data before October 2016 were used for the investigation of the prescription trends and the data after October 2016 were treated as references. Data analyses were conducted using SAS software (SAS Institute Inc., Cary, NC, USA).

2.3.2 Results

2.3.2.1 Patient characteristics

Characteristics of patients who had any prescription records for the psychotropic drugs are shown in Table 7. The proportions of female outpatients were higher than those of male outpatients. On the other hand, the proportions of female inpatients were slightly lower than those of male inpatients. The mean ages in both outpatients and inpatients aged < 65 years were 41–47, and those in both outpatients and inpatients aged ≥ 65 years were 76–78. The patient characteristics were stable throughout the study period in all patient groups.

Table 7. Patient characteristics

			Period 1	Period 2	Period 3	Period 4	Period 5
			Apr 2011 - Mar 2012	Apr 2012 - Mar 2014	Apr 2014 - Sep 2014	Oct 2014 - Mar 2016	Apr 2016 - Mar 2017
(a) Outpatients aged < 65 years		N	81,673	225,060	167,393	310,032	279,182
	Sex	Male (%)	44.9	45.0	44.7	44.9	45.0
		Female (%)	55.1	55.0	55.3	55.1	55.0
	Age [a]	Mean (SD)	43.7 (18.6)	41.5 (19.7)	42.8 (19.0)	40.6 (20.0)	41.3 (19.5)
		< 18 years (%)	12.5	16.2	14.4	17.8	16.7
		18-24 (%)	3.5	3.6	3.2	3.7	3.4
		25-34 (%)	9.4	9.3	8.4	8.8	8.3
		35-49 (%)	25.5	26.0	26.7	26.6	27.5
		50-64 (%)	49.0	44.8	47.3	43.1	44.1
		Over 65(%)	0	0	0	0	0
(b) Inpatients aged < 65 years		N	50,325	166,534	80,937	231,589	190,918
	Sex	Male (%)	53.1	51.3	51.8	51.4	50.5
		Female (%)	46.9	48.7	48.2	48.6	49.5
	Age [a]	Mean (SD)	46.5 (17.1)	45.3 (17.7)	44.8 (18.1)	44.6 (18.0)	44.9 (17.5)
		< 18 years (%)	8.4	9.7	10.7	10.7	9.9
		18-24 (%)	3.2	3.3	3.3	3.4	3.3
		25-34 (%)	8.9	9.3	9.0	9.1	9.0
		35-49 (%)	24.3	25.6	25.6	26.4	27.7
		50-64 (%)	55.3	52.1	51.5	50.5	50.2
		Over 65 (%)	0	0	0	0	0
(c) Outpatients aged ≥ 65 years		N	87,967	231,876	230,759	368,500	373,593
	Sex	Male (%)	42.0	42.4	41.0	41.4	41.7
		Female (%)	58.0	57.6	59.0	58.6	58.3
	Age [a,b]	Mean (SD)	75.6 (6.6)	75.5 (6.7)	76.1 (6.9)	75.9 (6.9)	76.2 (7.0)
		< 65 years (%)	0	0	0	0	0
		65-74 (%)	47.0	47.1	44.2	45.7	44.1
		Over 75 (%)	53.0	52.9	55.8	54.3	55.9
(d) Inpatients aged ≥ 65 years		N	82,835	286,081	152,304	453,429	415,855
	Sex	Male (%)	51.6	51.1	51.4	51.2	50.5
		Female (%)	48.4	48.9	48.6	48.8	49.5
	Age [a,b]	Mean (SD)	77.5 (7.3)	77.6 (7.4)	77.6 (7.5)	77.8 (7.6)	78.1 (7.6)
		< 65 years (%)	0	0	0	0	0
		65-74 (%)	37.6	37.3	37.5	36.8	35.4
		Over 75 (%)	62.4	62.7	62.5	63.2	64.6

N, total number of patients who were prescribed at least one psychotropic drug in each segmented period; SD, standard deviation.

[a] As of the initial month of prescription records for any psychotropic drugs in each segmented period.

[b] Ninety years old or more was counted as 90 years old at the time when data were provided from Medical Data Vision Co., Ltd.

2.3.2.2 Proportions of patients by the number of prescribed drugs

The observed changes of the proportions of patients by the number of prescribed drugs in 4 patient groups are shown in Table 8 and Appendix Figure 1.

(a) Outpatients aged < 65 years

The prescription trends in the outpatients aged < 65 years in the MDV database (Table 8(a)) were similar to those in the study population in the MinaCare database (Table 3) and there was a tendency that the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics decreased after the revisions of the polypharmacy reduction policy in 2014 and 2016, but not in BZs. The proportions of patients with 3 or more drugs in the outpatients aged < 65 years were decreased from April 2011 to March 2017 for anxiolytics (1.3%→1.1%), hypnotics (4.0%→2.9%), antidepressants (2.6%→1.6%), and antipsychotics (10.2%→8.4%), but increased in BZs (7.9%→9.2%) (Table 8(a)). The proportions of patients with monotherapy were increased from April 2011 to March 2017 only for antidepressants (82.0%→83.6%), and not changed or decreased for anxiolytics (88.5%→86.9%), hypnotics (82.2%→76.7%), antipsychotics (68.2%→68.3%), sum of anxiolytics and hypnotics (73.5%→68.5%), BZs (73.6%→69.7%), and sum of psychotropic drugs (62.4%→57.8%).

(b) Inpatients aged < 65 years

There was no clear and consistent tendency in the inpatients aged < 65 years that the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics decreased after the introduction or revisions of the policy (Table 8(b)). The proportions of patients with 3 or more drugs in the inpatients aged < 65 years were decreased from April 2011 to April 2016 for antidepressants (2.7%→2.2%) and BZs (6.9%→6.6%), and not changed or increased for anxiolytics (1.1%→1.2%), hypnotics (3.9%→4.6%), and antipsychotics (10.8%→12.1%) (Table 8(b)). The

proportions of patients with monotherapy were increased from April 2011 to April 2016 only for anxiolytics (87.9%→89.8%) and sum of anxiolytics and hypnotics (70.1%→71.4%), and not changed or decreased for hypnotics (80.9%→79.1%), antidepressants (83.8%→83.3%), antipsychotics (70.3%→67.3%), BZs (76.1%→76.8%), and sum of psychotropic drugs (64.2%→64.7%).

(c) Outpatients aged ≥ 65 years

There was a weak tendency that the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics decreased after the revisions of the polypharmacy reduction policy in 2014 and 2016 in the outpatients aged ≥ 65 years (Table 8(c)). However, the proportions of patients with 3 or more drugs in this population (Table 8(c)) were lower than those in the outpatients aged < 65 years (Table 8(a)), and the clear tendency of decrease was not observed. The proportions of patients with 3 or more drugs in the outpatients aged ≥ 65 years were decreased from April 2011 to March 2017 for anxiolytics (0.6%→0.4%) and antidepressants (1.1%→0.7%), and not changed or increased for hypnotics (1.0%→1.2%), antipsychotics (1.8%→1.9%), and BZs (3.2%→3.3%) (Table 8(c)). However, the proportion of patients with 3 or more hypnotics was decreased after the revision of the policy in October 2014 (from 1.4% in April 2014 to 1.1% in October 2014) and that with 3 or more antipsychotics was decreased after the revision of the policy in April 2016 (from 2.4% in Oct 2015 to 2.1% in April 2016). The proportions of patients with monotherapy in the outpatients aged ≥ 65 years were increased from April 2011 to March 2017 only for antidepressants (88.5%→89.8%), and not changed or decreased for anxiolytics (93.5%→93.0%), hypnotics (91.0%→87.3%), antipsychotics

(89.5%→86.9%), sum of anxiolytics and hypnotics (80.7%→78.0%), BZs (81.1%→80.3%), and sum of psychotropic drugs (74.7%→72.0%).

(d) Inpatients aged ≥ 65 years

There was no clear and consistent tendency in the inpatients aged ≥ 65 years that the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics decreased after the introduction or revisions of the policy (Table 8(d)). The proportions of patients with 3 or more drugs in the inpatients aged ≥ 65 years were decreased from April 2011 to April 2016 for anxiolytics (1.0%→0.6%) and BZs (4.1%→3.8%), and increased for hypnotics (1.8%→2.7%), antidepressants (0.9%→1.3%), and antipsychotics (3.1%→4.0%) (Table 8(d)). The proportions of patients with monotherapy were increased from April 2011 to April 2016 only for anxiolytics (89.2%→91.1%) and BZs (77.4%→78.8%), and not changed or decreased for hypnotics (85.4%→82.2%), antidepressants (92.0%→90.8%), antipsychotics (81.9%→78.4%), sum of anxiolytics and hypnotics (72.0%→72.1%), and sum of psychotropic drugs (63.3%→62.3%).

(e) Comparison between patient groups

For hypnotics, antidepressants, and antipsychotics, the proportions of patients with monotherapy were higher in both outpatients and inpatients aged ≥ 65 years than in those aged < 65 years (Table 8(a)–(d), Appendix Figure 1). For anxiolytics, sum of anxiolytics and hypnotics, BZs, and sum of psychotropic drugs, the proportions of patients with monotherapy were higher in the outpatients aged ≥ 65 years than in the outpatients aged < 65 years. On the other hand, the proportions of patients with

monotherapy were not so different between the inpatients aged < 65 years and those aged ≥ 65 years for anxiolytics, sum of anxiolytics and hypnotics, BZs, and sum of psychotropic drugs. In the patients aged ≥ 65 years, the proportion of outpatients with monotherapy was higher than that of inpatients for hypnotics, antipsychotics, sum of anxiolytics and hypnotics, and sum of psychotropic drugs. Except them, there were not so much differences in the proportions of patients with monotherapy between the outpatients and inpatients in the same age categories.

Table 8. Observed changes of psychotropic prescriptions by the number of prescribed drugs

(a) Outpatients aged < 65 years	Apr 2011	Oct 2011	Apr 2012	Oct 2012	Apr 2013	Oct 2013	Apr 2014	Oct 2014	Apr 2015	Oct 2015	Apr 2016	Oct 2016	Mar 2017
Anxiolytics (N)	11401	12688	12751	18002	23391	25212	36429	36438	40877	41674	43380	42937	45270
1	88.5	89.2	89.1	89.0	88.7	88.4	87.5	87.6	86.6	86.4	86.7	86.8	86.9
2	10.2	9.5	9.4	9.6	9.9	10.1	10.9	11.1	12.1	12.3	12.0	12.0	12.0
≥3	1.3	1.4	1.5	1.4	1.5	1.5	1.6	1.3	1.2	1.3	1.3	1.2	1.1
Hypnotics (N)	12428	13466	13831	19792	26804	29176	42248	43198	49161	50464	52836	53149	57002
1	82.2	82.2	81.8	81.2	80.0	80.1	78.5	79.1	77.0	77.1	76.5	76.8	76.7
2	13.8	13.9	14.2	14.8	15.3	15.4	16.4	17.3	19.7	19.7	20.1	20.1	20.3
≥3	4.0	3.9	4.0	4.0	4.7	4.5	5.0	3.6	3.4	3.2	3.5	3.1	2.9
Antidepressants (N)	4782	5228	5243	7808	10490	11650	16930	17260	20029	20907	22211	22863	25237
1	82.0	81.2	81.6	82.8	81.3	82.4	82.0	82.7	82.9	82.5	82.8	83.5	83.6
2	15.5	15.8	15.5	14.8	15.3	14.5	15.2	14.8	14.7	15.2	15.2	14.7	14.7
≥3	2.6	3.0	2.9	2.4	3.3	3.0	2.8	2.5	2.4	2.3	2.0	1.8	1.6
≥4	0.4	0.3	0.3	0.3	0.6	0.5	0.4	0.4	0.3	0.3	0.3	0.2	0.2
Antipsychotics (N)	5084	5260	5347	8007	10823	12529	18746	18996	23550	24269	25428	25690	27650
1	68.2	68.9	69.4	69.0	68.5	68.4	68.5	68.8	66.2	66.5	67.0	67.6	68.3
2	21.6	20.8	20.5	21.5	22.0	21.8	21.8	21.8	23.0	22.9	23.2	23.5	23.3
≥3	10.2	10.3	10.0	9.5	9.5	9.8	9.7	9.5	10.8	10.6	9.8	8.8	8.4
≥4	2.9	3.0	3.0	2.6	2.6	2.7	2.6	2.2	2.7	2.4	2.5	2.2	2.1
Sum of anxiolytics and hypnotics (N)	20301	22423	22820	32418	42805	46374	66069	67050	74912	76618	79944	79955	85148
1	73.5	74.4	74.4	73.8	72.7	72.6	70.4	70.9	68.7	68.6	68.4	68.6	68.5
2	18.2	17.6	17.5	18.0	18.4	18.7	19.6	19.6	20.7	20.8	20.9	20.7	21.0
≥3	8.3	8.0	8.1	8.2	8.8	8.8	10.0	9.5	10.6	10.6	10.8	10.6	10.4
BZs (N)	18476	20476	20691	29467	38323	41677	59123	59989	67234	68513	71089	70819	74966
1	73.6	75.0	74.8	74.3	72.8	72.7	70.7	71.2	69.2	69.1	69.5	69.8	69.7
2	18.5	17.4	17.5	18.1	18.8	19.0	19.8	19.8	20.9	21.1	20.8	20.7	21.0
≥3	7.9	7.6	7.7	7.6	8.4	8.3	9.5	9.0	9.9	9.8	9.7	9.5	9.2
Sum of psychotropic drugs (N)	23159	25475	25828	37134	48901	53603	76129	77630	86951	89308	93428	94401	101408
1	62.4	63.3	63.4	63.0	62.3	61.8	59.6	60.3	57.5	57.4	57.2	57.9	57.8
2	18.1	18.2	18.1	18.1	17.9	18.1	18.7	18.5	18.7	18.8	19.0	18.7	19.1
3	8.7	8.4	8.3	8.6	8.7	8.9	9.3	9.3	10.1	10.2	10.2	10.3	10.2
4	5.1	4.9	4.6	4.7	5.0	5.0	5.5	5.6	6.3	6.3	6.2	6.2	6.1
5	2.8	2.5	2.7	2.8	2.9	2.9	3.2	3.2	3.6	3.6	3.6	3.5	3.5
≥6	2.8	2.8	2.9	2.8	3.3	3.3	3.7	3.2	3.7	3.7	3.7	3.4	3.2

(b) Inpatients aged < 65 years	Apr 2011	Oct 2011	Apr 2012	Oct 2012	Apr 2013	Oct 2013	Apr 2014	Oct 2014	Apr 2015	Oct 2015	Apr 2016	Oct 2016	Mar 2017
Anxiolytics (N)	3319	3821	3848	5424	6828	7500	10028	10534	11187	11374	11775	13289	14265
1	87.9	88.7	88.0	89.1	88.9	88.9	89.9	89.1	89.8	89.2	89.8	88.0	88.2
2	11.0	10.2	10.7	9.8	10.0	10.0	9.1	9.9	9.2	9.7	9.0	10.5	10.5
≥3	1.1	1.1	1.3	1.1	1.1	1.2	1.0	1.0	1.1	1.0	1.2	1.5	1.3
Hypnotics (N)	3723	4334	4513	6361	8404	9112	12133	12479	13744	13860	14552	16888	17753
1	80.9	81.7	81.4	82.0	81.5	80.6	80.4	80.3	79.6	78.8	79.1	76.9	76.9
2	15.2	14.5	15.0	14.3	14.6	15.5	15.3	15.7	16.3	17.0	16.3	18.4	18.2
≥3	3.9	3.8	3.6	3.7	3.9	3.9	4.3	4.0	4.1	4.2	4.6	4.8	4.9
Antidepressants (N)	364	440	416	606	847	918	1304	1403	1500	1551	1815	2725	2930
1	83.8	83.6	85.6	85.3	83.6	83.9	85.3	83.3	81.5	83.3	83.3	79.5	81.3
2	13.5	13.4	12.0	11.9	13.6	13.6	11.7	14.0	16.1	14.2	14.5	18.1	16.6
≥3	2.7	3.0	2.4	2.8	2.8	2.5	3.0	2.7	2.5	2.5	2.2	2.4	2.2
≥4	0.5	0.7	0.2	0.3	0.7	0.4	0.5	0.4	0.3	0.1	0.3	0.2	0.4
Antipsychotics (N)	1090	1184	1287	1774	2317	2731	3611	3805	4292	4520	4782	6026	6120
1	70.3	70.9	73.1	73.0	70.0	69.9	71.0	69.4	65.9	65.4	67.3	65.8	65.7
2	18.9	18.5	18.6	17.7	20.2	20.4	18.8	20.2	21.7	21.4	20.6	22.2	23.2
≥3	10.8	10.6	8.2	9.3	9.9	9.7	10.2	10.4	12.4	13.1	12.1	11.9	11.1
≥4	3.5	3.7	2.8	2.6	3.1	3.3	3.0	2.9	4.1	4.3	4.1	3.5	3.7
Sum of anxiolytics and hypnotics (N)	5874	6791	6954	9920	12862	13990	18679	19352	20986	21193	22338	25100	26703
1	70.1	70.5	69.4	71.5	71.5	71.0	71.5	71.1	70.8	70.4	71.4	68.4	68.6
2	21.2	21.0	22.2	20.6	20.2	20.4	19.9	20.3	20.5	20.4	19.8	21.1	21.2
≥3	8.7	8.5	8.5	7.9	8.2	8.6	8.5	8.6	8.7	9.1	8.8	10.5	10.2
BZs (N)	4592	5318	5471	7693	10157	10943	14517	14764	16154	16307	17003	19516	20445
1	76.1	75.5	75.8	76.9	76.7	76.0	76.6	75.8	76.1	75.2	76.8	73.7	73.9
2	17.1	17.6	17.9	17.1	17.1	17.2	16.6	17.2	17.0	17.6	16.6	18.0	18.3
≥3	6.9	6.9	6.3	6.0	6.3	6.8	6.8	7.0	6.9	7.1	6.6	8.2	7.8
Sum of psychotropic drugs (N)	6181	7136	7348	10427	13634	14831	19827	20588	22269	22560	23937	26954	28736
1	64.2	64.6	63.8	65.2	65.8	65.1	65.2	64.7	64.3	63.9	64.7	60.6	61.4
2	20.2	20.6	21.2	20.3	19.8	19.8	19.8	20.0	19.5	19.2	18.9	19.7	19.8
3	7.8	6.9	8.0	7.6	6.9	7.2	7.2	7.2	7.3	7.5	7.5	8.4	8.3
4	3.6	3.6	3.5	3.3	3.3	3.6	3.5	3.8	4.0	4.1	3.9	5.0	4.5
5	2.0	2.0	1.5	1.6	1.9	1.8	2.1	2.0	2.2	2.4	2.3	2.8	2.7
≥6	2.3	2.3	2.0	2.0	2.2	2.5	2.3	2.4	2.6	2.8	2.7	3.5	3.3

(c) Outpatients aged ≥ 65 years	Apr 2011	Oct 2011	Apr 2012	Oct 2012	Apr 2013	Oct 2013	Apr 2014	Oct 2014	Apr 2015	Oct 2015	Apr 2016	Oct 2016	Mar 2017
Anxiolytics (N)	15349	16950	17575	24163	31713	34948	52628	54107	60214	61608	64977	61853	65929
1	93.5	93.3	93.1	93.0	93.4	93.5	93.0	93.1	92.6	92.6	92.6	92.7	93.0
2	5.9	6.2	6.5	6.5	6.2	6.0	6.5	6.4	7.0	7.0	7.0	6.9	6.6
≥3	0.6	0.5	0.5	0.5	0.5	0.4	0.5	0.5	0.5	0.5	0.5	0.4	0.4
Hypnotics (N)	22065	23896	25805	34853	47764	52856	78160	81592	93844	95770	105168	104146	112113
1	91.0	90.9	90.5	90.7	89.8	89.7	88.7	88.8	88.2	88.3	87.8	87.7	87.3
2	8.0	8.1	8.4	8.3	8.9	9.0	9.8	10.1	10.7	10.7	11.1	11.2	11.6
≥3	1.0	1.0	1.1	1.1	1.2	1.3	1.4	1.1	1.1	1.0	1.1	1.1	1.2
Antidepressants (N)	4478	4741	5058	7464	9921	11132	16684	17524	19981	20742	22631	23715	26231
1	88.5	88.1	88.7	88.5	88.3	88.6	88.2	88.7	88.5	88.8	89.2	89.6	89.8
2	10.4	10.5	10.2	10.3	10.4	10.3	10.7	10.2	10.2	10.1	9.8	9.7	9.5
≥3	1.1	1.4	1.0	1.2	1.3	1.1	1.2	1.1	1.2	1.1	1.0	0.8	0.7
≥4	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1
Antipsychotics (N)	3166	3398	3576	5090	6830	7709	11971	12565	15109	15404	16905	16884	17945
1	89.5	89.0	89.1	88.8	88.5	88.5	88.1	88.1	86.8	86.8	86.8	86.7	86.9
2	8.7	9.2	9.1	9.2	9.6	9.6	10.1	10.1	11.0	10.9	11.1	11.4	11.2
≥3	1.8	1.9	1.8	2.0	1.9	1.9	1.9	1.8	2.2	2.4	2.1	1.9	1.9
≥4	0.2	0.3	0.4	0.4	0.2	0.3	0.3	0.2	0.2	0.3	0.3	0.2	0.3
Sum of anxiolytics and hypnotics (N)	32949	36022	38252	52283	70292	77623	114491	119144	134720	137811	149029	145876	156232
1	80.7	80.6	80.3	80.8	80.4	80.2	78.8	79.2	78.3	78.5	78.1	78.4	78.0
2	15.9	15.9	16.2	15.8	16.0	16.2	16.9	16.8	17.4	17.3	17.6	17.4	17.8
≥3	3.5	3.4	3.5	3.4	3.6	3.6	4.2	4.0	4.3	4.2	4.3	4.2	4.2
BZs (N)	32055	34894	37004	50512	67742	74832	110137	114533	129251	131884	141461	137737	146315
1	81.1	81.2	81.1	81.8	81.5	81.3	80.1	80.5	79.8	80.0	80.1	80.5	80.3
2	15.6	15.7	15.8	15.3	15.4	15.6	16.3	16.1	16.6	16.4	16.4	16.1	16.4
≥3	3.2	3.1	3.1	3.0	3.1	3.1	3.6	3.4	3.6	3.5	3.5	3.4	3.3
Sum of psychotropic drugs (N)	35781	39115	41598	57056	76621	84731	124592	130142	147077	150729	163406	161330	173708
1	74.7	74.9	74.7	74.7	74.5	74.2	72.7	73.0	71.9	72.1	72.0	72.2	72.0
2	17.4	17.4	17.5	17.3	17.4	17.6	18.1	18.1	18.5	18.4	18.4	18.3	18.6
3	5.0	4.8	4.9	5.0	5.0	5.1	5.6	5.5	5.9	5.8	5.9	5.9	5.9
4	1.8	1.8	1.7	1.9	1.9	2.0	2.2	2.1	2.3	2.2	2.3	2.3	2.2
5	0.7	0.6	0.6	0.7	0.8	0.7	0.9	0.8	0.9	0.9	0.9	0.9	0.8
≥6	0.5	0.4	0.4	0.4	0.5	0.5	0.6	0.5	0.5	0.5	0.5	0.5	0.5

(d) Inpatients aged ≥ 65 years	Apr 2011	Oct 2011	Apr 2012	Oct 2012	Apr 2013	Oct 2013	Apr 2014	Oct 2014	Apr 2015	Oct 2015	Apr 2016	Oct 2016	Mar 2017
Anxiolytics (N)	5583	6027	6404	9116	11957	13476	18289	19757	20940	21607	23323	27533	29392
1	89.2	89.6	89.6	89.6	90.4	90.1	90.3	90.3	90.5	90.9	91.1	89.5	90.1
2	9.7	9.5	9.7	9.7	8.8	9.1	8.9	9.0	8.9	8.5	8.3	9.7	9.1
≥3	1.0	0.9	0.7	0.7	0.8	0.8	0.8	0.6	0.6	0.6	0.6	0.8	0.8
Hypnotics (N)	7062	7952	8867	12129	17045	18347	26589	26977	31755	32339	37079	44411	48847
1	85.4	85.2	84.7	84.6	84.6	84.2	83.4	83.8	83.2	82.9	82.2	80.7	80.0
2	12.8	12.7	13.2	13.1	13.1	13.3	14.0	14.0	14.4	14.7	15.1	16.4	16.8
≥3	1.8	2.0	2.1	2.3	2.3	2.4	2.6	2.2	2.5	2.4	2.7	2.9	3.2
Antidepressants (N)	804	940	1020	1563	2068	2199	3330	3478	3946	4276	5039	7112	8306
1	92.0	90.5	89.8	88.8	90.1	90.5	90.5	91.2	90.2	90.6	90.8	90.4	90.7
2	7.1	8.6	8.6	9.7	8.8	8.6	8.2	7.5	8.6	8.5	8.0	8.8	8.5
≥3	0.9	0.9	1.6	1.5	1.1	0.9	1.3	1.3	1.2	0.9	1.3	0.8	0.8
≥4	0	0	0	0.1	0.2	0.1	0.1	0.2	0.2	0.1	0.1	0.1	0.1
Antipsychotics (N)	2544	2853	3294	4541	6336	6939	10031	10568	12300	12752	14412	16839	18560
1	81.9	82.1	83.3	81.2	80.1	80.4	79.4	78.8	78.3	78.6	78.4	78.7	78.1
2	15.0	14.6	13.6	15.6	16.7	16.3	17.0	17.4	17.7	17.4	17.5	17.2	17.7
≥3	3.1	3.3	3.1	3.2	3.2	3.4	3.6	3.8	4.0	4.0	4.0	4.1	4.1
≥4	0.3	0.3	0.5	0.3	0.6	0.4	0.6	0.6	0.7	0.6	0.5	0.6	0.6
Sum of anxiolytics and hypnotics (N)	10601	11791	12914	17949	24645	27016	37976	39633	44852	45889	51617	60839	66224
1	72.0	72.6	72.3	72.2	72.9	72.8	71.8	72.4	72.3	72.2	72.1	69.8	69.5
2	21.3	20.9	21.1	21.1	20.7	20.6	21.3	21.2	21.1	21.3	21.3	22.7	22.9
≥3	6.7	6.6	6.6	6.7	6.4	6.6	6.8	6.5	6.6	6.6	6.6	7.5	7.6
BZs (N)	8945	10004	10930	15121	20867	22788	32161	33034	37821	38179	42347	50667	54567
1	77.4	78.2	77.8	78.1	78.7	78.4	77.3	78.0	78.5	78.2	78.8	76.4	76.7
2	18.5	17.4	18.1	17.5	17.4	17.3	18.3	17.7	17.4	17.8	17.4	19.0	18.9
≥3	4.1	4.4	4.1	4.4	3.9	4.3	4.4	4.2	4.2	4.1	3.8	4.6	4.4
Sum of psychotropic drugs (N)	11651	13003	14367	19981	27507	30021	42444	44433	50333	51582	58226	68600	74867
1	63.3	64.1	63.8	63.5	63.8	63.6	62.6	63.0	62.6	62.4	62.3	59.9	59.4
2	23.3	22.4	22.8	22.7	22.8	22.8	23.2	23.2	23.0	23.0	23.3	24.3	24.4
3	8.1	8.2	8.2	8.5	8.3	8.2	8.6	8.5	8.8	8.9	8.6	9.4	9.5
4	3.4	3.2	3.1	3.3	3.0	3.2	3.3	3.2	3.3	3.5	3.5	3.8	4.0
5	1.2	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.4	1.4	1.4	1.6	1.6
≥6	0.7	0.8	0.7	0.8	0.8	0.9	0.9	0.9	0.8	0.9	0.9	1.0	1.1

BZ, benzodiazepine receptor agonist; N, total number of patients who were prescribed at least one drug within the drug category in each month; sum of psychotropic drugs, sum of anxiolytics, hypnotics, antidepressants, and antipsychotics. Values displayed are proportions of patients (%). Total number of patients who were prescribed at least one drug within the drug category in each month was used as a denominator.

2.3.2.3 Means of the average daily doses

The observed changes of the means of the average daily doses are plotted in Figure 6. There were no noticeable decreases after the policy introduction or revisions for all patient groups in any drug categories. For sum of anxiolytics and hypnotics as well as BZs, the means of the average daily doses were lower in both the outpatients and the inpatients aged ≥ 65 years than in those aged < 65 years as well as lower in the inpatients than in the outpatients. For antidepressants, the means of the average daily doses were lower in both the outpatients and the inpatients aged ≥ 65 years than in those aged < 65 years, but there were little differences between the outpatients and the inpatients in the same age categories. In addition, the means of the average daily doses in antidepressants were increased throughout the study period in all patient groups. For antipsychotics, the means of the average daily doses were lower in both the outpatients and the inpatients aged ≥ 65 years than in those aged < 65 years as well as lower in the outpatients than in the inpatients. In the inpatients, the means of the average daily doses for sum of anxiolytics and hypnotics, BZs, and antidepressants were steeply increased after October 2016.

2.3.2.4 Proportions of patients above clinically recommended doses

The observed changes of the proportions of patients above clinically recommended doses are plotted in Figure 7. The decreases of the proportions of patients above clinically recommended doses were identified only for the inpatients (both aged < 65 years and aged ≥ 65 years) in antipsychotics throughout the study period. For sum of anxiolytics and hypnotics as well as BZs, the proportions of patients above clinically recommended doses were lower in both the outpatients and the inpatients aged ≥ 65

years than in those aged < 65 years as well as lower in the inpatients than in the outpatients. The proportions of patients above clinically recommended doses in antidepressants were increased throughout the study period in all patient groups. For antipsychotics, the proportions of patients above clinically recommended doses were much higher in the inpatients than in the outpatients, and there was little difference between the inpatients aged < 65 years and those aged ≥ 65 years. In the inpatients, the proportions of patients above clinically recommended doses for sum of anxiolytics and hypnotics, BZs, and antidepressants were steeply increased after October 2016.

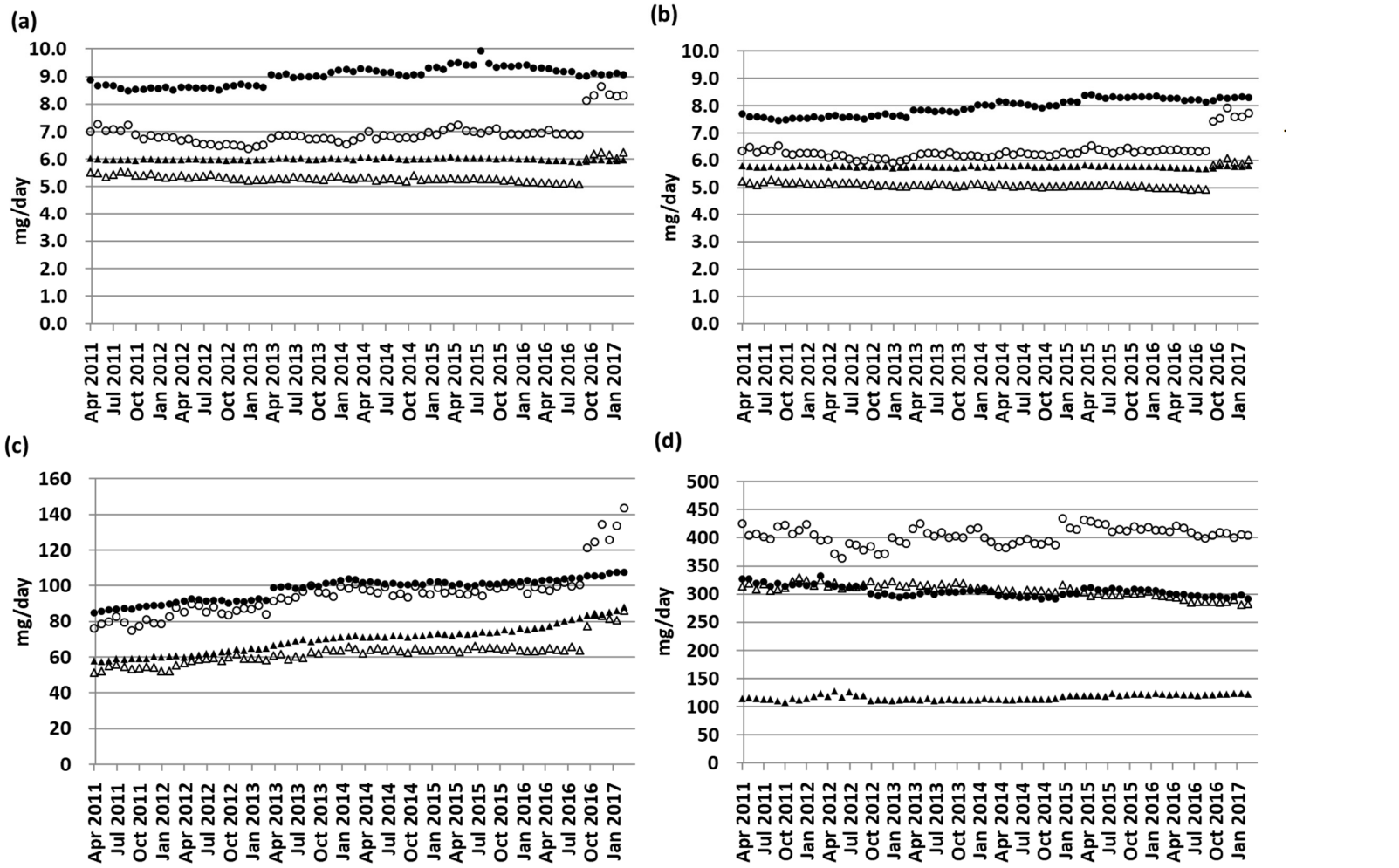


Figure 6. Observed changes of the means of the average daily doses: (a) sum of anxiolytics and hypnotics, (b) BZs, (c) antidepressants, and (d) antipsychotics. Diazepam-equivalent doses for anxiolytics and hypnotics as well as BZs, imipramine-equivalent doses for antidepressants, and chlorpromazine-equivalent doses for antipsychotics were used. BZ, benzodiazepine receptor agonist.

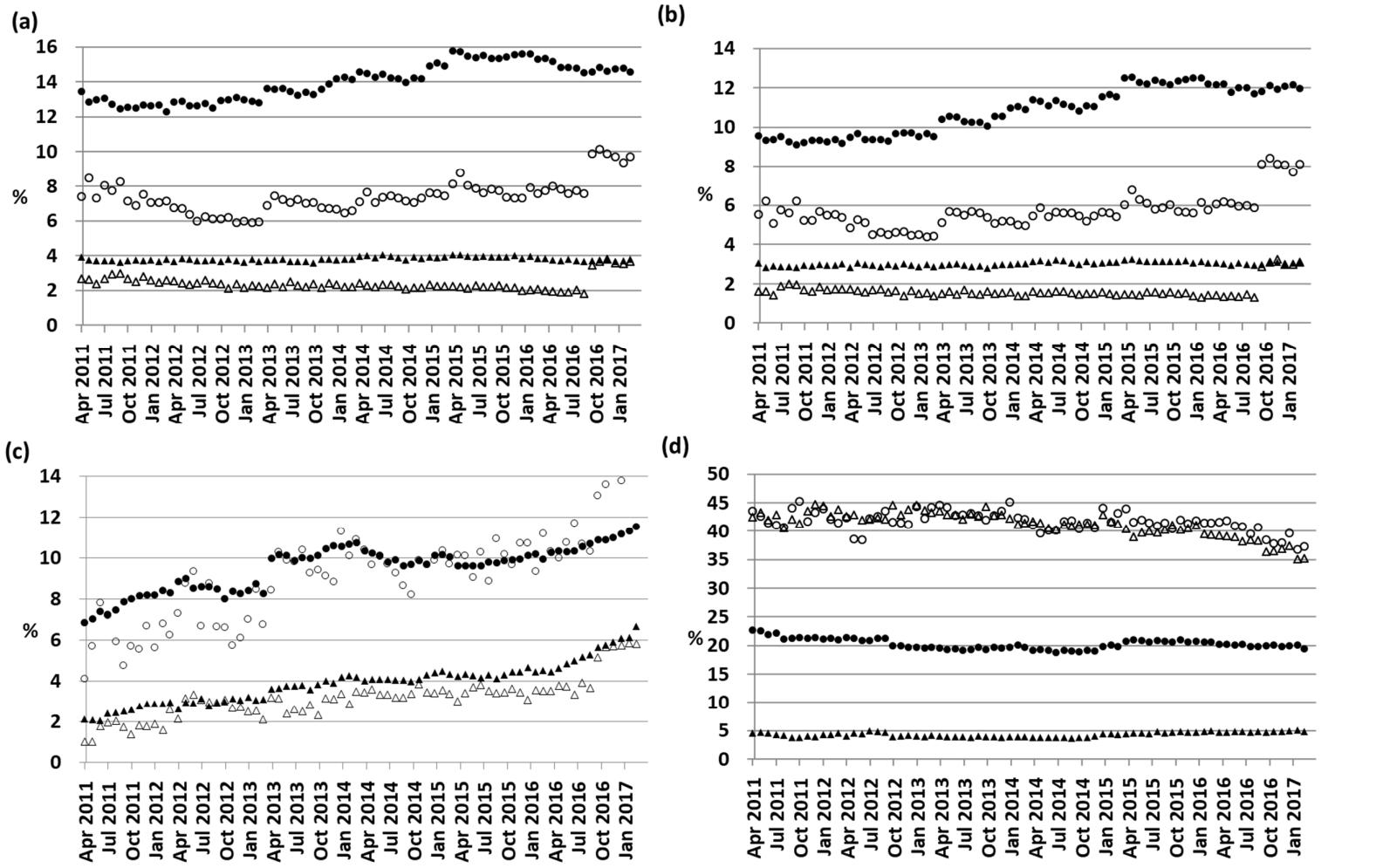


Figure 7. Observed changes of the proportions of patients above clinically recommended doses: (a) sum of anxiolytics and hypnotics, (b) BZs, (c) antidepressants, and (d) antipsychotics. Diazepam-equivalent doses for anxiolytics and hypnotics as well as BZs, imipramine-equivalent doses for antidepressants, and chlorpromazine-equivalent doses for antipsychotics were used. BZ, benzodiazepine receptor agonist.

2.4 Discussion

2.4.1 Research 1-1 Investigation into changes in prescription of psychotropic drugs after introduction of polypharmacy reduction policy based on the MinaCare database

In Research 1-1, we examined the effect of the polypharmacy reduction policy on psychotropic prescriptions using the MinaCare database. The policy led to significant drops in the proportions of patients with 3 or more drugs in all categories of the psychotropic drugs (anxiolytics, hypnotics, antidepressants, and antipsychotics). The results of the analysis in patient-level supported these results. On the other hand, there were no significant drops in the proportions of patients with 3 or more BZs after the policy introduction in 2012 as well as after the notification and enforcement of the revision in 2014. The change in the trend of the proportion of patients with 3 or more BZs after the introduction of the policy in April 2012 was thought to be due to the changes of prescriptions of anxiolytics and hypnotics, but there were no significant drops after April 2012. The proportions of patients with monotherapy were increased from April 2011 to March 2017 only for antidepressants and antipsychotics, and not changed or decreased for anxiolytics, hypnotics, sum of anxiolytics and hypnotics, BZs, and sum of psychotropic drugs. The proportions of patients with 2 or more drugs in March 2017 were still 14.3%, 22.4%, 19.2%, and 17.9% in anxiolytics, hypnotics, antidepressants, antipsychotics, and 34.3%, 32.7%, and 50.1% in sum of anxiolytics and hypnotics, BZs, and sum of psychotropic drugs, respectively.

The study using a large and representative sample of visits to office-based psychiatrists in the United States reported that the proportions of patients with 2 or more drugs in 2005-2006 were 17.8%, 25.4%, and 14.9% in sedative-hypnotics, antidepressants, and antipsychotics, respectively [2]. The study using Australian

pharmaceutical claims data showed that the proportions of patients with 2 or more drugs in 2015 were 3.7%, 7.3%, and 2.9% in antidepressants, antipsychotics, and BZs, respectively [46]. The Research on Asian Psychotropic Prescription Patterns (REAP) for antidepressants reported that the proportions of patients with 2 or more antidepressants were 3–25% in 5 East Asian countries in 2004 [47]. These figures cannot be compared directly because the databases, populations, and study periods were different, but the proportions of patients with 2 or more drugs within the drug category in Japan did not seem to be lower than these countries even in 2017.

In Japan, the high rate of antipsychotic polypharmacy compared with other countries has been known for a few decades [48, 49], and some clinical trials were conducted to simplify antipsychotic prescription in Japan [50–52]. There had been efforts to reduce antipsychotic polypharmacy, but drastic measures to address it had been needed. The polypharmacy reduction policy reduced antipsychotic polypharmacy and the mean daily dose of antipsychotics. The decreasing trend shown in the present study corresponded with the other report [49]. However, the REAP for antipsychotics in 2016 indicated that the rate of psychotropic polypharmacy including within- and between-drug categories and high-dose treatment for schizophrenia patients was the highest in Japan among 15 Asian countries/areas [28, 53], and further improvement would be needed.

The polypharmacy reduction policy in Japan had not had a reduction rule for the category of BZs before April 2018. BZs were separately classified as anxiolytics or hypnotics, and therefore, if 2 BZs of anxiolytics and 1 BZ of hypnotics were prescribed at one time, fees reduction was not applied. In the present study, there were no significant drops in the proportions of patients with 3 or more BZs after the policy introduction in 2012 and the notification and enforcement of the revision in 2014. The reduction policy should be applied to polypharmacy of BZs since they have similar

mechanisms of action and safety profiles.

Various policies to reduce the prescription of BZs were introduced in Western countries. In the United States, Medicare Part D, which is a prescription drug coverage program, excluded BZs from coverage in 2006 [54, 55]. In the Netherlands, BZs were excluded from the Dutch reimbursement list when used as anxiolytics, hypnotics, or sedatives in 2009 [56, 57]. Furthermore, in France, the new payment system started in 2012, in which general practitioners could receive monetary benefit in the case that they reduced the prescription of BZs in some criteria [58]. In the Netherlands case, the prescription of BZs was decreased, but in the United States and the France cases, the prescription of BZs was not decreased. There are limitations to compare these policies because the policy characteristics and environment are different between countries, but some political intervention will be needed in Japan based on the lessons from other countries. Actually, in Japan, the new reduction rule for BZs was introduced in April 2018, in which the reimbursement rates of the prescription fees are reduced by about 30–40% if BZs are prescribed for more than 12 months with the same dosage and regimen [20]. This fees reduction seemed to be applied in April 2019 when 12 months passed after the rule was enforced. The effect of this rule needs to be investigated, but there is some doubt about the effect because this fees reduction is not applied if the dosage or regimen of BZs is changed within 12 months.

In the present study, the proportions of patients above clinically recommended doses were increased or not changed between March 2014 (before the notification of the revision in 2014) and March 2017 for sum of anxiolytics and hypnotics, BZs, and antidepressants although there were some ups and downs. For antipsychotics, the proportion of patients above clinically recommended doses was decreased after the revision in April 2016. There were immediate increases in the levels of the

proportions of patients above clinically recommended doses for sum of anxiolytics and hypnotics as well as BZs after the notification of the revision in April 2014. The increases of the means of the average daily doses were also identified at that time. The temporal increases of the doses by switching of medications seemed to be one of the reasons. This tendency corresponded with the other report [23]. The effect of the policy in reducing the proportions of patients above clinically recommended doses was identified in antipsychotics after the policy revision in 2016, but not identified in sum of anxiolytics and hypnotics as well as BZs after the notification and enforcement of the revision in 2014, and antidepressants after the revision in 2016. Thus, in the present study, only limited effects were seen for reducing the proportions of patients above clinically recommended doses although the proportions of patients with 3 or more drugs were decreased after the introduction or revisions of the polypharmacy reduction policy. In addition, even in the patients with monotherapy or 2 drugs, not a few patients (7–12%) were prescribed more than clinically recommended doses throughout the study period. The Japanese package inserts in some psychotropic drugs say that the dosage may be adjusted depending on the patient's age and symptoms and do not set the upper limits of the doses. This may be one of the reasons of high-dose prescription of the psychotropic drugs. The rule considering total doses in addition to the number of prescribed drugs should be taken into account in this policy. The means of the average daily doses in sum of anxiolytics and hypnotics as well as BZs were decreased after April 2016, although there was no policy revision for anxiolytics and hypnotics at that time. Further investigation is needed to examine the trend after March 2017.

The proportions of patients who were prescribed 2 or more drugs within the same drug subclass in the patients who were prescribed 2 or more drugs were 89.6%–94.4%, 10.3–16.9%, and 61.5–68.4% in sum of anxiolytics and hypnotics, antidepressants, and

antipsychotics, respectively. This result shows that not a few patients were prescribed several drugs within the same drug subclasses.

The proportion of patients with nonpharmacological treatments (< 2.0%) was much lower than that with psychotropic prescriptions (16.6–28.9%) throughout the study period. These results indicate that pharmacological treatments are much more common than nonpharmacological treatments in Japan. In the Japanese guidelines for major depressive disorders [31] and insomnia [32], CBT and sleep hygiene education are recommended as the first-line therapy or combination therapy with pharmacological treatments. A systematic review examining the treatment effects of second generation antidepressants and CBT suggested no difference among them, either alone or in combination [59]. A long-term randomized trial indicated that CBT for insomnia, when delivered alone or in combination with pharmacotherapy, produced durable sleep improvements up to two years after completion of treatment [60]. In addition, there is a report which suggests that young and middle-age insomnia patients can derive significantly greater benefit from CBT than pharmacotherapy [61]. These results suggest that CBT is an important alternative to pharmacotherapy or makes it possible to taper medication. However, CBT for insomnia including sleep hygiene education is not covered by health insurance [32, 62] in Japan. Hence, the sites and therapists which/who can provide these nonpharmacological treatments are very limited [62]. Environmental improvement for expanding these nonpharmacological treatments such as establishment of their insurance reimbursement and incentive fees as well as nurturing these therapists are important.

2.4.2 Research 1-2 Investigation into trends in prescription of psychotropic drugs in DPC hospitals based on the MDV database

In Research 1-2, we supplementarily examined the trends in psychotropic prescriptions in DPC hospitals by age (< 65 year-old/ ≥ 65 year-old) and outpatients/inpatients using the MDV database. The prescription trends in the outpatients aged < 65 years in the MDV database were similar to those in the study population in the MinaCare database. There was a tendency that the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics were decreased after the revisions of the polypharmacy reduction policy in 2014 and 2016, but not in BZs in the outpatients aged < 65 years. The similar tendency was observed in the outpatients aged ≥ 65 years, but it was not so clear because the proportions of patients with 3 or more drugs in this population were lower than those in the outpatients aged < 65 years. There was no clear and consistent tendency in the inpatients that the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics were decreased after the introduction or revisions of the policy. This might be due to the fact that the policy is not applied to the inpatients. In addition, the proportions of monotherapy were not changed so much and there were no noticeable decreases of the means of the average daily doses for all patient groups in any drug categories. The decreases of the proportions of patients above clinically recommended doses were identified only for the inpatients in antipsychotics throughout the study period.

The proportions of patients with monotherapy were generally higher in the patients aged ≥ 65 years than in those aged < 65 years. This trend corresponded with the other reports [2, 63]. The means of the average daily doses were consistently lower in the patients aged ≥ 65 years than in the patients aged < 65 years. Careful administration of the psychotropic drugs for elderly is alerted in most of their Japanese package inserts. Some psychotropic drugs are recommended to be started and continued at lower doses

than non-elderly. This might be the reason that the means of the average daily doses were lower in the patients aged ≥ 65 years than in the patients aged < 65 years. The proportions of patients above clinically recommended doses generally showed similar tendency to the means of the average daily doses except the inpatients who were prescribed antipsychotics. In the inpatients who were prescribed antipsychotics, the proportions of patients above clinically recommended doses were not different between the patients aged < 65 years and those aged ≥ 65 years. High-dose antipsychotics might be used for the inpatients because antipsychotics induces sedation especially at high doses [64]. Generally, there was no noticeable issue in psychotropic prescriptions specific for the elderly.

In the inpatients, the means of the average daily doses as well as the proportions of patients above clinically recommended doses for sum of anxiolytics and hypnotics, BZs, and antidepressants were steeply increased after October 2016. This might be due to the fact that entry of the information of medications which inpatients bring themselves on the DPC data became mandatory in October 2016 [45].

2.4.3 Chapter summary

In Research 1-1, the effect of the polypharmacy reduction policy reducing the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics was identified, but not in BZs. On the other hand, only limited effects were seen for increasing the proportions of monotherapy and reducing the proportions of patients above clinically recommended doses. In addition, not a few patients were prescribed more than clinically recommended doses even in the patients with monotherapy or 2 drugs, and not a few patients were prescribed several drugs within the same drug subclass throughout the study period. The proportion of patients

with nonpharmacological treatments was much lower than that with psychotropic prescriptions throughout the study period. In Research 1-2, the prescription trends in the outpatients in the DPC hospitals supported the results in Research 1-1. On the other hand, there was no clear and consistent tendency of decrease in the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics in the inpatients. This might be due to the fact that the policy was not applied to the inpatients. There was no noticeable issue in psychotropic prescriptions specific for the elderly.

There are some limitations in this study. First, the results might have been biased because of changes in the study population and simultaneously occurring other intervention [65]. However, the patient characteristics were stable during the study period, and especially, in Research 1-1, the sensitivity analysis restricted to the patients who were continuously enrolled in the database during the study period yielded similar results. In addition, other interventions, if any, should not have had a big enough impact to reverse the effect of the polypharmacy reduction policy because this policy is the only one to penalize prescribers. Second, drugs prescribed in each month was regarded as a simultaneous prescription and the prescriptions based on psychiatry/ non-psychiatry could not be evaluated separately. In addition, in Research 1-1, we did not evaluate out-of-hospital/ in-hospital prescriptions separately. However, we think it is important to examine whole prescriptions for each patient using the claims data which includes all prescribed drugs covered by the health insurance system to evaluate the actual condition of psychotropic polypharmacy. Third, in Research 1-1, the effect of the introduction of the policy in 2012 on the proportions of patients above clinically recommended doses and the mean daily doses for sum of anxiolytics and hypnotics as well as BZs could not be evaluated because of the lack of information before April 2012.

However, the effect of the policy revision in 2014 on the proportions of patients above clinically recommended doses and the means of the average daily doses could be evaluated. As the rule of the fees reduction in 2014 was much stricter than that in 2012 (Table 1), our study did cover the most important parts of the policies. Fourth, in Research 1-2, it is impossible to compare the prescription trends between before October 2016 and after then for inpatients because the data entry rule for medications which the inpatients bring was changed in October 2016 [45]. However, the most important objective in Research 1-2 was to compare the prescription trends between elderly and non-elderly. We could compare them even though there was the change of the data entry rule. Fifth, any effectiveness indicators such as disease improvement or deterioration, rates of adverse events, medical resource utilization, and medical cost were not investigated. Further investigation is needed to examine the effect of the policy on these true outcomes.

3. Research 2 Influence of psychotropic polypharmacy on safety events

3.1 Background

Psychotropic polypharmacy is common in clinical practice [2–4] mainly because of perceived inadequate response to monotherapy, although supporting evidence is limited [3, 7–10]. It is reported that psychotropic polypharmacy increases the risk of adverse events compared to monotherapy [2, 9, 14]. An Australian literature review revealed that people taking more than one antipsychotic at a time are more likely to experience adverse events than those taking only one antipsychotic at a time [14]. Pharmacoepidemiological studies using large-scale healthcare databases, which allow to follow cohorts of several million persons have gained attention as drug safety surveillance and signal detection [66]. However, there are few pharmacoepidemiological studies which examined the influence of psychotropic polypharmacy on safety events. The most common limitation in traditional methodologies for evaluating exposure-outcome associations, such as cohort or case-control studies is that they require data on a large number of confounders to produce unbiased risk estimates [66, 67]. In the claims database, available information of confounders is limited, which becomes a major barrier to conduct pharmacoepidemiological studies using claims databases. A sequence symmetry analysis (SSA) is a self-controlled study design [68, 69], and has major advantages that it is easy to process and it is robust towards confounders that are stable over time.

In Research 2, the influence of psychotropic polypharmacy on safety events was examined based on the SSA using the MinaCare database. We selected the safety events which were reported to be associated with use of the psychotropic drugs and whose occurrence could be defined with claims data. It was reported that use of some antidepressants is associated with hypertension [70, 71] and extrapyramidal syndromes

(EPS) [72–75], and use of some antipsychotics is associated with diabetes mellitus [76, 77], pneumonia [78], EPS [79], hyperlipidemia [77, 80], and acute myocardial infarction [81]. Moreover, BZs are reported to increase risk of hip fracture [82]. These events could be defined with claims data based on both a diagnosis of the event and a prescription of therapeutic drug/ medical procedure for the event; therefore, these events were selected for the events of interest.

3.2 Methods

3.2.1 Data Source

Monthly administrative claims data including pharmacy claims, medical claims, and DPC claims provided by MinaCare Co., Ltd. between April 2011 to March 2016 were used. For details on this database, see Section 2.2.1.1 “Data Source” of Methods in Research 1-1.

3.2.2 Sequence symmetry analysis

An SSA, a self-controlled study design [68, 69] was used to examine the influence of psychotropic polypharmacy on the events of interest. SSA examines asymmetry in the distribution of an outcome before and after an exposure of interest. Asymmetry may indicate an association of the exposure of interest with the outcome.

The ratio of patients who experienced an outcome after the exposure of interest (exposure→outcome) to those who experienced an outcome before the exposure of interest (outcome→exposure) was defined as the crude sequence ratio (CSR). SSA could be sensitive to prescribing trends, such as a rapid increase in marker drug use and a trend in polypharmacy, over time. A null-effect sequence ratio (NSR) was calculated to adjust the CSR for the background rates of the exposure and the outcome according

to the method described in the original proposal for the SSA [68, 69]. The underlying assumption is that in the absence of a causal association, the exposure and the outcome would follow the same incidence pattern as observed in the background population (that is, all population in the database). The probability for the exposure to precede the outcome (that is, exposure→outcome), in the absence of any causal relationship, can be estimated in a NSR. By dividing the CSR by the NSR, an adjusted sequence ratio (ASR) was obtained. The 95% confidence interval (CI) for the ASR was also calculated based on binomial distributions [69, 83]. The ASR can be similar to the incidence rate ratio of the outcome in exposed to non-exposed person-time if both the exposures and outcomes are uniformly distributed over the observation period [68]. The advantage of SSA is that it is robust to confounders that are stable over time, e.g., sex, and genetic factors [69]. If confounders such as lifestyle habits, body mass index, and medical history do not vary substantially throughout the observation period, their confounding effects would be minimized because these factors would not affect the assumption of symmetry [84]. Furthermore, the effect of time-varying confounders can be reduced by limiting an evaluation time window [67].

3.2.3 Exposure

An exposure was defined as a prescription for each category (anxiolytics, hypnotics, antidepressants, and antipsychotics) of the psychotropic drugs. The initial month in which the exposure was identified was defined as an "exposure month". The classification of the psychotropic drugs was based on the Japanese polypharmacy reduction policy revised in 2016 (Appendix Table 1) [33]. Patients were divided into 3 groups according to the number of prescribed drugs (1, 2, and 3 or more) for each category of the psychotropic drugs at the exposure month, and an SSA was conducted

by the number of prescribed drugs. The number of prescribed drugs was counted based on generic names regardless of formulation.

A separate analysis in which anxiolytics and hypnotics were summed was conducted when any significant signal was found in anxiolytics or hypnotics, since some BZs are classified as anxiolytics and others are as hypnotics (Appendix Table 1). That is, the initial month of a prescription for any anxiolytics and hypnotics was defined as an exposure month for the category of sum of anxiolytics and hypnotics, and an SSA was conducted by the number of anxiolytics and hypnotics at the exposure month. An analysis by the number of BZs at the exposure month was also conducted. The analysis by the number of BZs was restricted to patients who did not use anxiolytics and hypnotics other than BZs during the study period.

3.2.4 Outcome

Hypertension, diabetes mellitus, pneumonia, EPS, hyperlipidemia, bone fracture, and acute myocardial infarction were selected for the safety events of interest. For hypertension, diabetes mellitus, pneumonia, EPS, and hyperlipidemia, an outcome was defined as both a diagnosis of the event and a prescription of therapeutic drug for the event in the same month. For bone fracture and acute myocardial infarction, an outcome was defined as both a diagnosis of the event and a medical procedure for the event in the same month. Diagnoses were coded according to the International Classification of Diseases, 10^{th} revision (ICD-10) codes. Outcome definition of each event was described in Appendix Table 4. The initial month in which the outcome was identified was defined as an “outcome occurrence month”. It was reported that the definition of an outcome based on both a diagnosis and a prescription was validated and more precise than either the definition based on only a diagnosis or that based on only a

prescription in a validation study of the Medical Information for Risk Assessment Initiative (MIHARI) project by the Pharmaceuticals and Medical Devices Agency in Japan [85]. An analysis in which an outcome was defined only by prescription of therapeutic drug for the event as well as an analysis in which an outcome was defined only by diagnosis of the event were conducted as sensitivity analyses.

3.2.5 Study population

An SSA was performed for the patients who experienced both the exposure and the outcome. The analysis was restricted to patients who had their first exposure and outcome after a run-in period of 6 months to exclude prevalent users of the psychotropic drugs and prevalent event cases, which was defined as an analysis set [67, 68].

To reduce the effect of time-varying confounders [67], intervals between the exposure month and the outcome occurrence month were restricted to 3, 6, and 12 months (primary interval: 12 months). The initial time point of an evaluation window was the exposure month or the outcome occurrence month, whichever came first. The patients whose initial exposure and outcome occurred in the same month were excluded from calculation of the sequence ratio as previous reports [86, 87] because the sequence of the exposure and outcome could not be determined.

In the analyses for hyperlipidemia, patients who had any prescription records of gamma oryzanol during the study period were excluded because gamma oryzanol is categorized as an anxiolytic as well as has an indication for treatment of hyperlipidemia.

3.2.6 Evaluation of subclass effects of psychotropic drugs on safety events

Analyses by subclasses of the psychotropic drugs were also conducted if any significant signal was found in any drug categories of the psychotropic drugs. The

classification of the subclasses is described in Appendix Table 1.

In the SSA, switching drugs might affect the estimation of the background rate from the non-causal sequences. In the present study, only the first prescription within a category at the exposure month was counted, as Lai proposed [67]. For example, if a patient started taking a typical antipsychotic and then changed to an atypical antipsychotic after the next month, the atypical antipsychotic prescription was not considered a new start and was excluded from analyses. Garrison also reported their study results using this procedure [88]. Furthermore, the analysis was restricted to use of only one subclass during the study period in each category to assess probable effect of each subclass.

3.2.7 Additional analyses for EPS

For EPS, an additional analysis was conducted for patients who were prescribed anxiolytics, hypnotics, or antidepressants and were not prescribed antipsychotics during the study period (antipsychotics non-users) because antipsychotics were thought to be associated with a higher risk of EPS than anxiolytics, hypnotics, and antidepressants. In addition, the risk of antipsychotics-induced EPS is reported to increase dose-dependently [89–91]. Hence, total daily doses of typical and atypical antipsychotics at the exposure month were calculated. Furthermore, the analysis by the mean of the average daily doses (within or above clinically recommended doses) was conducted for the categories of sum of anxiolytics and hypnotics, BZs, antidepressants, and antipsychotics. The mean of the average daily doses was calculated in the procedure described in Section 2.2.1.3. The upper limit of the clinically recommended dose in each drug category was also defined in Section 2.2.1.3.

Data analyses were conducted using R versions 3.3.3 and 3.4.1 (R Foundation for

Statistical Computing, Vienna, Austria).

3.3 Results

All categories of the psychotropic drugs (anxiolytics, hypnotics, antidepressants, and antipsychotics) were significantly associated with EPS, and the tendency was stronger as the number of prescribed drugs was increased. BZs are mainstay anxiolytics/hypnotics, and a clearer association between polypharmacy of BZs and EPS was indicated. In addition, it was suggested that prescription of 2 or more BZs was associated with hyperlipidemia. On the other hand, the results for hypertension, diabetes mellitus, and pneumonia found no clear and consistent signals in any drug categories of the psychotropic drugs (data not shown). For bone fracture and acute myocardial infarction, the analysis in which an outcome was defined by only diagnosis of the event was firstly conducted and showed no clear and consistent signals in any drug categories of the psychotropic drugs (data not shown). Hence, the analysis in which an outcome was defined as both a diagnosis of the event and a medical procedure for the event in the same month was not conducted. The detailed results for EPS and hyperlipidemia are shown in the following sections.

3.3.1 EPS

The flow diagram of the study population for EPS is shown in Figure 8. A total of 1,978, 1,847, 1,367, and 2,015 patients were identified as analysis sets for anxiolytics, hypnotics, antidepressants, and antipsychotics, respectively. The characteristics of the analysis sets are shown in Table 9. The proportions of female patients were slightly higher than those of male patients and mean ages were around 40 years in all categories of the psychotropic drugs. Approximately 10–20% patients (anxiolytics: 10.8%,

hypnotics: 19.7%, antidepressants: 10.7%, antipsychotics: 21.1%) received concurrent prescription of multiple drugs for each category of the psychotropic drugs at the exposure month.

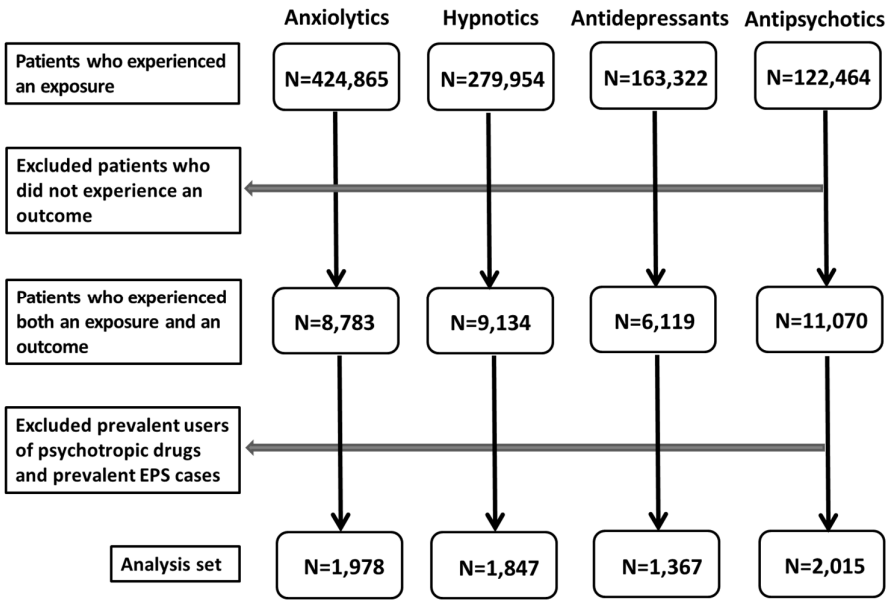


Figure 8. Flow diagram of study population for EPS

An exposure was defined as a prescription for each category of the psychotropic drugs. An outcome was defined as both a diagnosis of EPS and a prescription for antiparkinsonian drugs in the same month.
EPS, extrapyramidal syndromes.

Table 9. Patient characteristics for EPS analysis

		Anxiolytics (N=1,978)	Hypnotics (N=1,847)	Antidepressants (N=1,367)	Antipsychotics (N=2,015)
Sex	Male	907 (45.9)	853 (46.2)	643 (47.0)	947 (47.0)
	Female	1,071 (54.1)	994 (53.8)	724 (53.0)	1,068 (53.0)
Age [a]	Mean (SD)	39.1 (15.5)	39.4 (16.0)	38.4 (15.2)	37.5 (15.1)
	< 18 years	150 (7.6)	141 (7.6)	108 (7.9)	189 (9.4)
	18-24	229 (11.6)	215 (11.6)	173 (12.7)	241 (12.0)
	25-34	423 (21.4)	400 (21.7)	301 (22.0)	460 (22.8)
	35-49	694 (35.1)	614 (33.2)	467 (34.2)	704 (34.9)
	50-64	325 (16.4)	299 (16.2)	224 (16.4)	293 (14.5)
	65-74	157 (7.9)	178 (9.6)	94 (6.9)	128 (6.4)
Number of prescribed drugs for each category [a]	1	1,764 (89.2)	1,484 (80.3)	1,221 (89.3)	1,590 (78.9)
	2	187 (9.5)	312 (16.9)	122 (8.9)	312 (15.5)
	≥3	27 (1.4)	51 (2.8)	24 (1.8)	113 (5.6)

EPS, extrapyramidal syndromes; SD, standard deviation.
Values displayed are numbers of patients (%).
[a] As of the initial month of prescription records for each category of the psychotropic drugs (i.e., as of the exposure month).

The results of SSA found that all categories of the psychotropic drugs were significantly associated with EPS (Figure 9). The ASRs tended to be higher as the number of prescribed drugs at the exposure month was increased in all categories. The 95% CIs for 1 anxiolytic (ASR 2.48; 95% CI 2.16–2.85) and 2 anxiolytics (ASR 4.83; 95% CI 2.92–8.38), and those for 1 antidepressant (ASR 2.26; 95% CI 1.93–2.66) and 2 antidepressants (ASR 5.61; 95% CI 3.01–11.4) at the 12-month interval were not overlapped, respectively. Other 95% CIs were overlapped in each category because sample size was getting smaller as the number of prescribed drugs was increased. The analyses using different intervals (that is, 3 months and 6 months) yielded similar results (data not shown).

In the analysis in which anxiolytics and hypnotics were summed, the ASRs were clearly higher as the number of prescribed anxiolytics/hypnotics at the exposure month was increased (Figure 10(a)). BZs were mainstay anxiolytics/hypnotics as expected, and the analysis by the number of BZs yielded similar results (Figure 10(b)). In addition, the analyses for antipsychotics non-users also found that anxiolytics, hypnotics,

and antidepressants were significantly associated with EPS (data not shown).

The results of the analyses by subclasses of the psychotropic drugs are shown in Figure 11. In sum of anxiolytics and hypnotics, only BZs (ASR 3.40; 95% CI 2.89–4.01) were significantly associated with EPS (Figure 11(a)). In antidepressants, tetracyclic antidepressants (ASR 2.03; 95% CI 1.15–3.67), SSRIs (ASR 1.78; 95% CI 1.35–2.36), and SNRIs (ASR 1.76; 95% CI 1.05–2.98) were significantly associated with EPS (Figure 11(b)). Both typical and atypical antipsychotics were significantly associated with EPS (Figure 11(c)). The ASR of atypical antipsychotics (ASR 11.3; 95% CI 7.95–16.4) was higher than that of typical ones (ASR 2.96; 95% CI 2.06–4.33) and their 95% CIs were not overlapped. The chlorpromazine-equivalent total daily dose of typical antipsychotics at the exposure month was 76.5 mg/day, and that of atypical ones was 216.3 mg/day. The sensitivity analysis in which an outcome was defined only by prescription of therapeutic drug for the event or only by diagnosis of the event yielded similar results (data not shown).

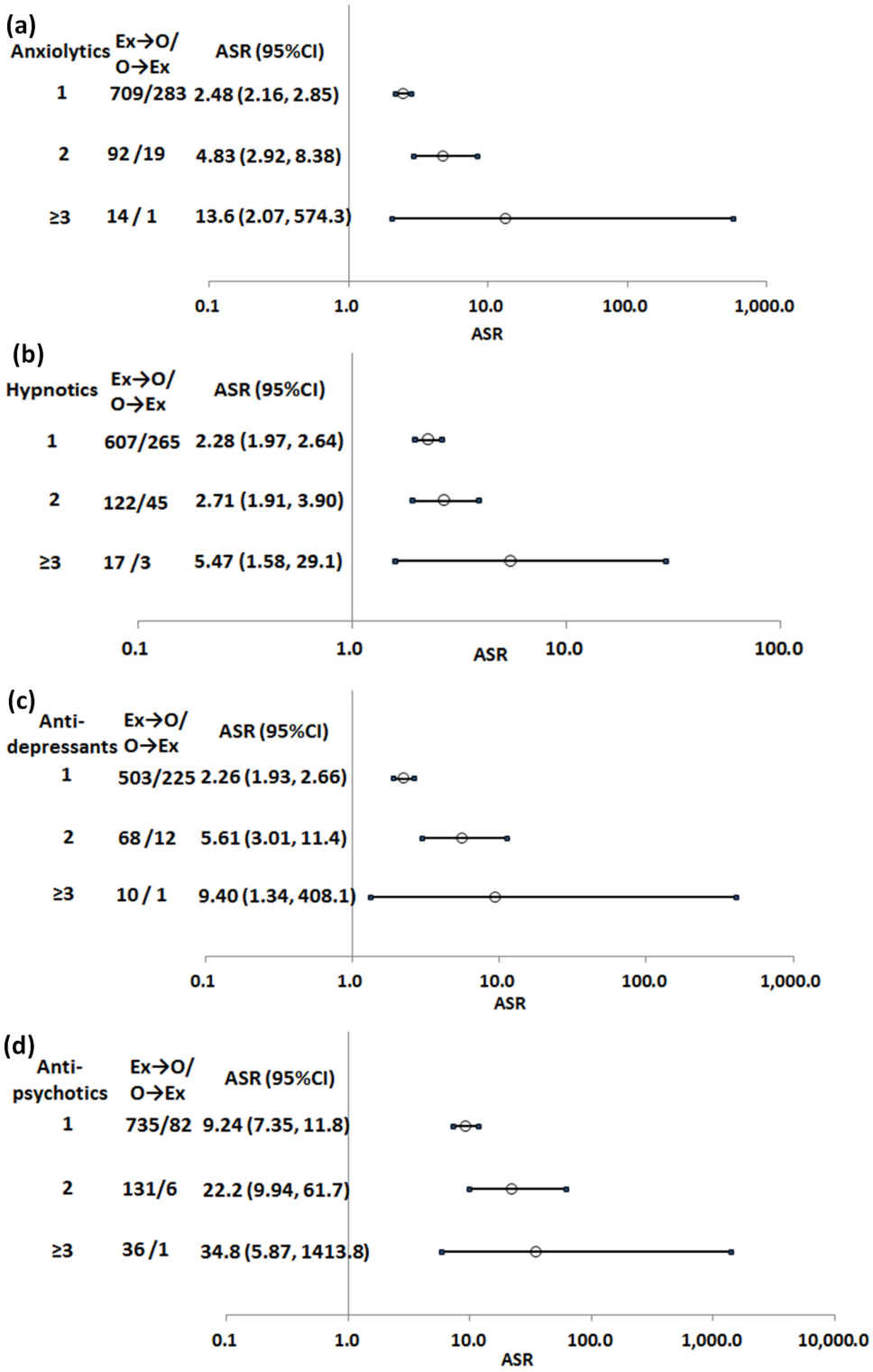


Figure 9. Results of SSA for EPS by the number of prescribed drugs at the exposure month for (a) anxiolytics, (b) hypnotics, (c) antidepressants, and (d) antipsychotics

An outcome was defined as both a diagnosis of EPS and a prescription for antiparkinsonian drugs in the same month. The interval between the exposure month and the outcome occurrence month was 12 months.
ASR, adjusted sequence ratio; CI, confidence interval; EPS, extrapyramidal syndromes; Ex, exposure; O, outcome; SSA, sequence symmetry analysis.

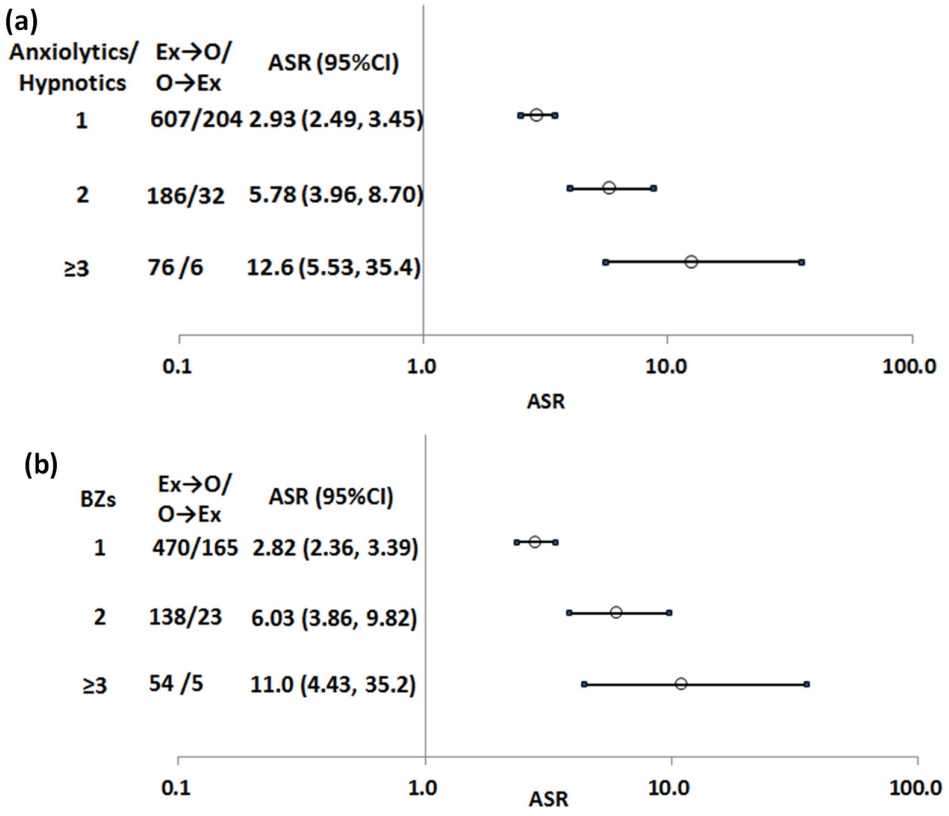


Figure 10. Results of SSA for EPS by the number of prescribed drugs at the exposure month for (a) sum of anxiolytics and hypnotics and (b) BZs

An outcome was defined as both a diagnosis of EPS and a prescription for antiparkinsonian drugs in the same month. The interval between the exposure month and the outcome occurrence month was 12 months.
ASR, adjusted sequence ratio; BZ, benzodiazepine receptor agonist; CI, confidence interval; EPS, extrapyramidal syndromes; Ex, exposure; O, outcome; SSA, sequence symmetry analysis.

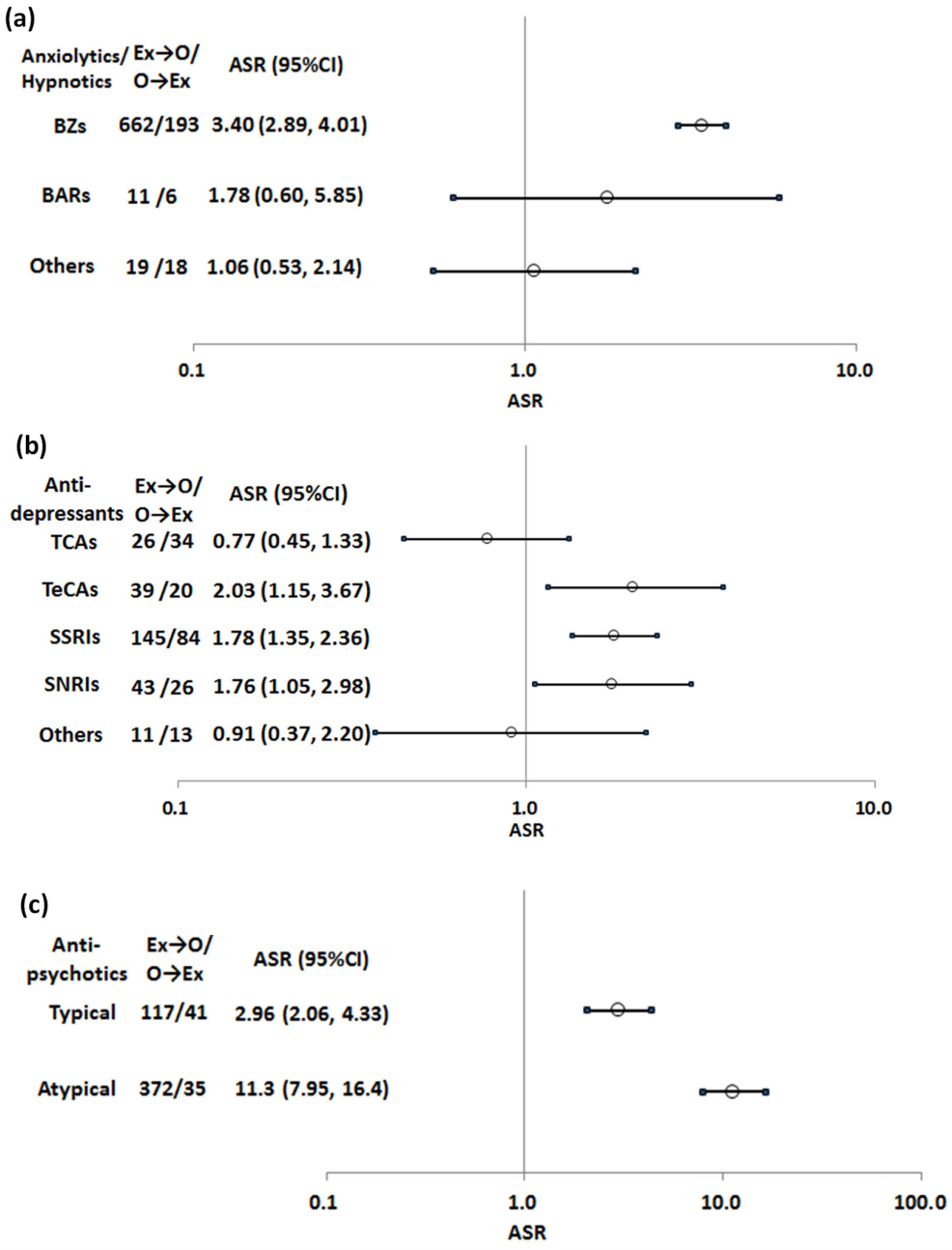


Figure 11. Results of SSA for EPS by subclasses: (a) sum of anxiolytics and hypnotics, (b) antidepressants, and (c) antipsychotics.

An outcome was defined as both a diagnosis of EPS and a prescription for antiparkinsonian drugs in the same month. The interval between the exposure month and the outcome occurrence month was 12 months.
ASR, adjusted sequence ratio; BAR, barbiturate and non-barbiturate; BZ, benzodiazepine receptor agonist; CI, confidence interval; EPS, extrapyramidal syndromes; Ex, exposure; O, outcome; SNRI, serotonin norepinephrine reuptake inhibitor; SSA, sequence symmetry analysis; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant.

The results of the analysis by the mean of average daily doses (within or above clinically recommended doses) are shown in Table 10. There was a tendency that the ASRs in the patients above clinically recommended doses were higher than those in the patients within clinically recommended doses in all categories.

Table 10. Results of SSA for EPS by the mean of average daily doses (within or above clinically recommended doses)

Drug category	Mean of average daily doses	Exposure→ Outcome Total (1/ 2/ ≥3) [a]	Outcome→ Exposure (Total/ 1/ 2/ ≥3) [a]	ASR	95% CI lower [b]	95% CI upper [b]
Sum of anxiolytics and hypnotics	≤ 15 mg/day	566 (446/ 98/ 22)	153 (134/ 16/ 3)	3.65	3.05	4.40
	> 15 mg/day	189 (78/ 67/ 44)	42 (31/ 8/ 3)	4.48	3.19	6.42
BZs	≤ 15 mg/day	459 (367/ 77/ 15)	140 (125/ 13/ 2)	3.26	2.69	3.97
	> 15 mg/day	154 (65/ 55/ 34)	38 (28/ 7/ 3)	4.09	2.85	6.00
Antidepressants	≤ 200 mg/day	558 (495/ 59/ 4)	226 (216/ 9/ 1)	2.51	2.15	2.94
	> 200 mg/day	14 (2/ 8/ 4)	3 (2/ 1/ 0)	4.43	1.24	24.1
Antipsychotics	≤ 450 mg/day	796 (700/ 87/ 9)	82 (78/ 4/ 0)	10.1	8.05	12.9
	> 450 mg/day	87 (29/ 35/ 23)	7 (4/ 2/ 1)	13.4	6.22	34.2

ASR, adjusted sequence ratio; BZ, benzodiazepine receptor agonist; CI, confidence interval; EPS, extrapyramidal syndromes; SSA, sequence symmetry analysis.
An outcome was defined as both a diagnosis of EPS and a prescription for antiparkinsonian drugs in the same month. The interval between the exposure month and the outcome occurrence month was 12 months. Diazepam-equivalent doses for anxiolytics and hypnotics as well as BZs, imipramine-equivalent doses for antidepressants, and chlorpromazine-equivalent doses for antipsychotics were used.
[a] Number of patients by the number of prescribed drugs.
[b] 95% CIs of ASRs are shown.

3.3.2 Hyperlipidemia

The flow diagram of the study population for hyperlipidemia is shown in Figure 12. A total of 10,493, 7,664, 2,988, and 2,715 patients were identified as analysis sets for anxiolytics, hypnotics, antidepressants, and antipsychotics, respectively. The characteristics of the analysis sets are shown in Table 11. The proportions of male patients were higher than those of female patients and mean ages were around 50 years in all categories of the psychotropic drugs. Less than 10% patients (anxiolytics: 5.6%,

hypnotics: 6.1%, antidepressants: 8.6%, antipsychotics: 4.1%) received concurrent prescription of multiple drugs for each category of the psychotropic drugs at the exposure month.

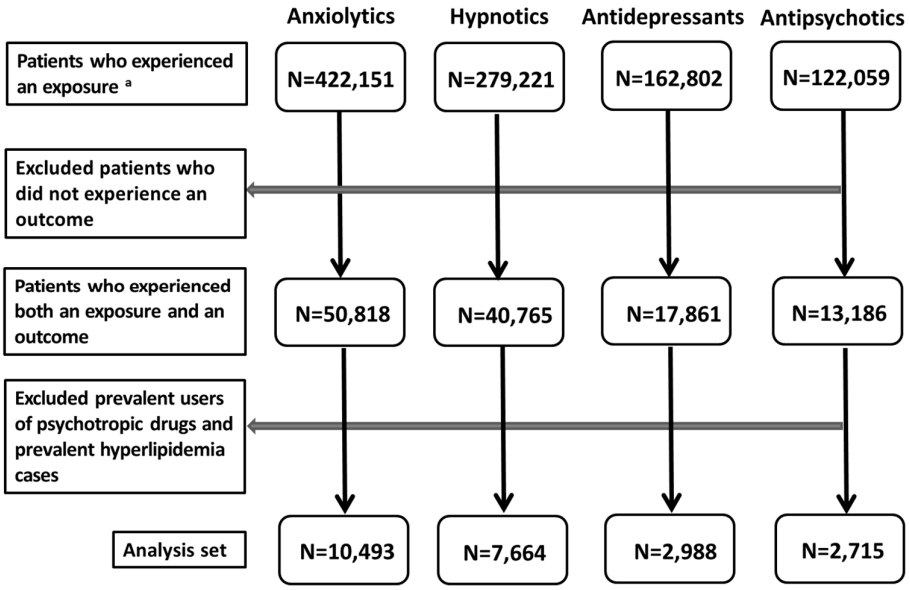


Figure 12. Flow diagram of study population for hyperlipidemia

An exposure was defined as a prescription for each category of the psychotropic drugs. An outcome was defined as both a diagnosis of hyperlipidemia and a prescription for antihyperlipidemic drugs in the same month.

[a] Gamma oryzanol, one of anxiolytics, also has an indication for treatment of hyperlipidemia. Patients who had any prescription records of gamma oryzanol were excluded from the analysis.

Table 11. Patient characteristics for hyperlipidemia analysis

		Anxiolytics (N=10,493)	Hypnotics (N=7,664)	Antidepressants (N=2,988)	Antipsychotics (N=2,715)
Sex	Male	5,531 (52.7)	4,205 (54.9)	1,871 (62.6)	1,637 (60.3)
	Female	4,962 (47.3)	3,459 (45.1)	1,117 (37.4)	1,078 (39.7)
Age [a]	Mean (SD)	53.2 (11.2)	53.7 (11.4)	48.8 (11.2)	49.5 (11.9)
	< 18 years	19 (0.2)	14 (0.2)	6 (0.2)	14 (0.5)
	18-24	60 (0.6)	58 (0.8)	39 (1.3)	33 (1.2)
	25-34	429 (4.1)	307 (4.0)	236 (7.9)	203 (7.5)
	35-49	3,473 (33.1)	2,371 (30.9)	1,347 (45.1)	1,150 (42.4)
	50-64	4,598 (43.8)	3,354 (43.8)	1,039 (34.8)	966 (35.6)
	65-74	1,914 (18.2)	1,560 (20.4)	321 (10.7)	349 (12.9)
Number of prescribed drugs for each category [a]	1	9,906 (94.4)	7,196 (93.9)	2,731 (91.4)	2,605 (95.9)
	2	546 (5.2)	427 (5.6)	231 (7.7)	96 (3.5)
	≥3	38 (0.4)	41 (0.5)	26 (0.9)	14 (0.5)

SD, standard deviation.
Values displayed are numbers of patients (%).
[a] As of the initial month of prescription records for each category of the psychotropic drugs (i.e., as of the exposure month).

There were no consistent signals in any drug categories of the psychotropic drugs varying the number of prescribed drugs (1, 2, and 3 or more) although it was found that the prescription of antidepressants or antipsychotics was associated with hyperlipidemia (data not shown). In the analysis in which anxiolytics and hypnotics were summed, prescription of 2 or more anxiolytics/hypnotics was associated with hyperlipidemia (Figure 13(a)). The analysis by the number of BZs yielded similar results (Figure 12(b)). The results of the analyses by subclasses of the psychotropic drugs are shown in Figure 14. In sum of anxiolytics and hypnotics, there were no signals in any subclasses (Figure 14(a)). SSRIs (ASR 1.40; 95% CI 1.18–1.65) and atypical antipsychotics (ASR 1.27; 95% CI 1.002–1.61) were significantly associated with hyperlipidemia (Figure 14(b), (c)).

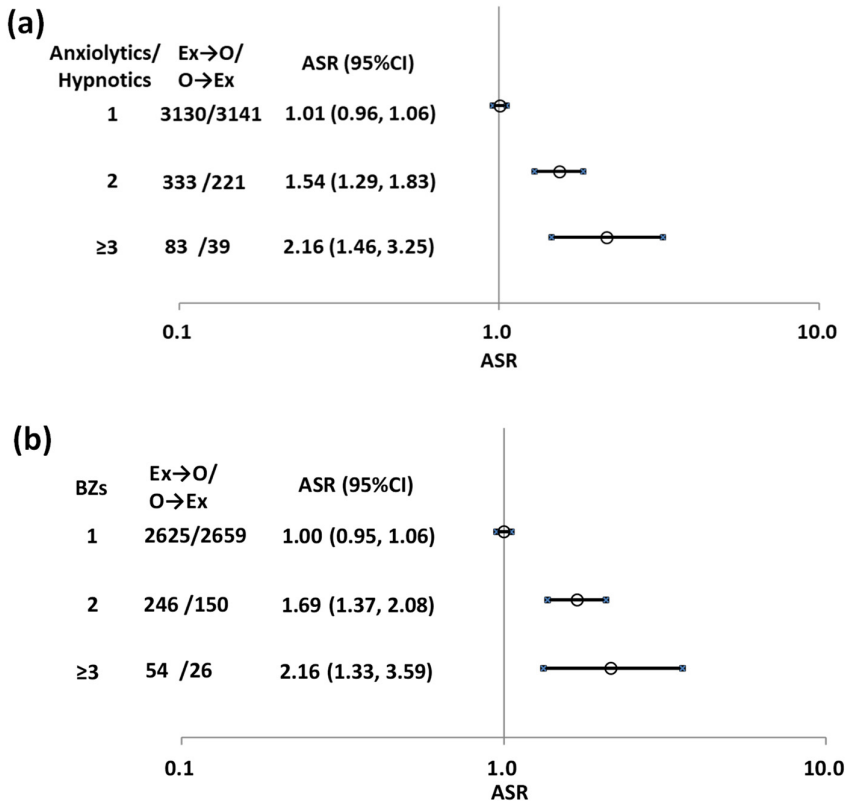


Figure 13. Results of SSA for hyperlipidemia by the number of prescribed drugs at the exposure month for (a) sum of anxiolytics and hypnotics and (b) BZs

An outcome was defined as both a diagnosis of hyperlipidemia and a prescription for antihyperlipidemic drugs in the same month. The interval between the exposure month and the outcome occurrence month was 12 months.

ASR, adjusted sequence ratio; BZ, benzodiazepine receptor agonist; CI, confidence interval; Ex, exposure; O, outcome; SSA, sequence symmetry analysis.

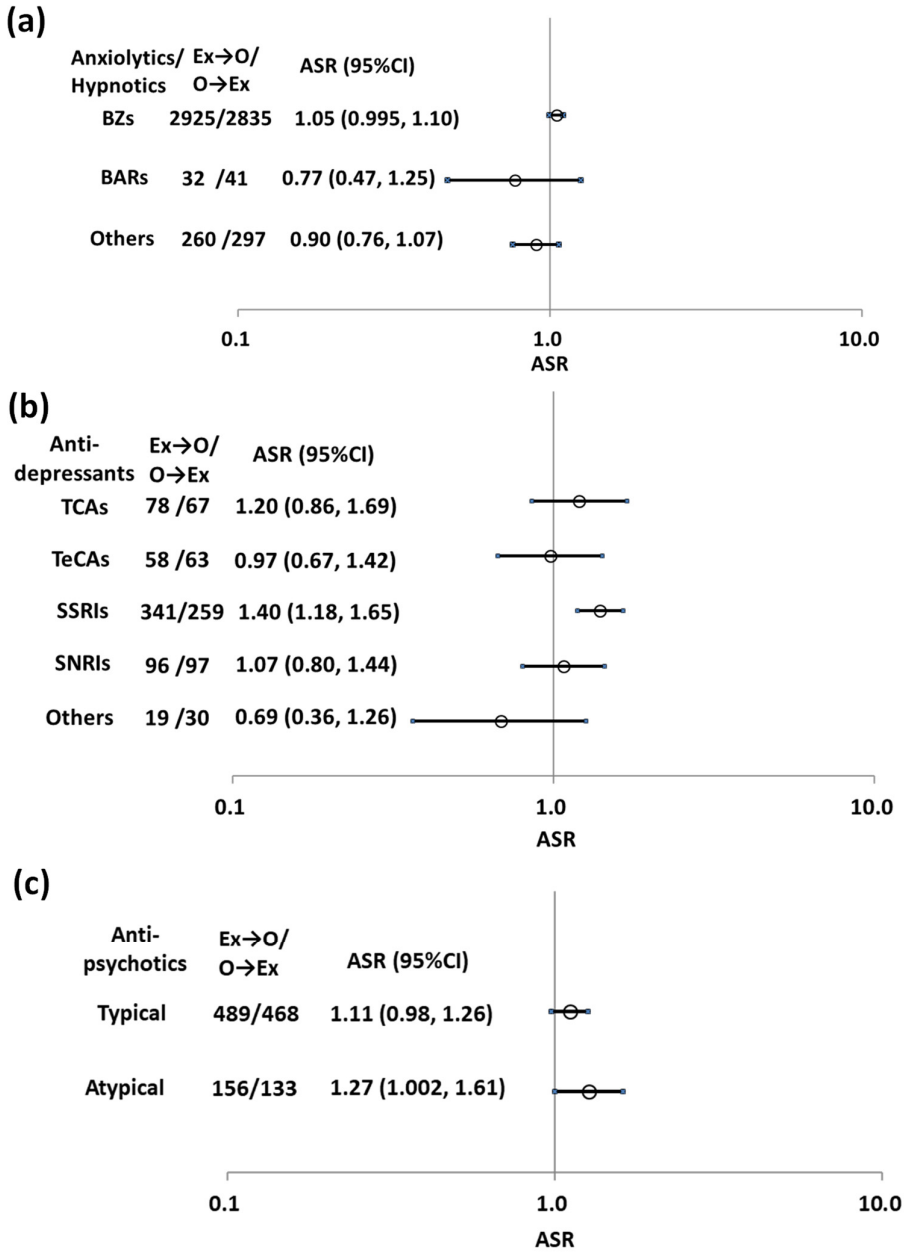


Figure 14. Results of SSA for hyperlipidemia by subclasses: (a) sum of anxiolytics and hypnotics, (b) antidepressants, and (c) antipsychotics.
An outcome was defined as both a diagnosis of hyperlipidemia and a prescription for antihyperlipidemic drugs in the same month. The interval between the exposure month and the outcome occurrence month was 12 months.
ASR, adjusted sequence ratio; BAR, barbiturate and non-barbiturate; BZ, benzodiazepine receptor agonist; CI, confidence interval; Ex, exposure; O, outcome; SNRI, serotonin norepinephrine reuptake inhibitor; SSA, sequence symmetry analysis; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant.

3.4 Discussion

3.4.1 EPS

All categories of the psychotropic drugs (anxiolytics, hypnotics, antidepressants, and antipsychotics) were significantly associated with EPS. The risk of EPS tended to be higher as the number of prescribed drugs for each category was increased although most 95% CIs of ASRs were overlapped. The analysis of summed anxiolytics and hypnotics showed a clearer association between polypharmacy of BZs and EPS. Moreover, in the analyses by subclasses of the psychotropic drugs, BZs, tetracyclic antidepressants, SSRIs, SNRIs, and typical and atypical antipsychotics were significantly associated with EPS.

BZs are said to induce movement disorders due to facilitation of the inhibitory effects of gamma-aminobutyric acid (GABA) through binding $GABA_A$ receptors [92, 93]. Hence, EPS are recognized adverse events of BZs; however, they are rare, and there are few published case reports [94]. Cochrane Database of Systematic Reviews said that in treatment of psychosis-induced aggression or agitation, BZs produce EPS less frequently as compared with typical antipsychotics, but can cause respiratory depression, ataxia, excessive sedation, memory impairment, and paradoxical disinhibition [95–97]. In the present study, the association between BZs and EPS was indicated and the risk was increased due to polypharmacy.

Furthermore, the association between SSRIs and EPS was suggested, which corresponded with previous reports [72–75]. The mechanisms responsible for EPS may be related to excessive levels of serotonin, which may disrupt dopaminergic neurons in the nigrostriatal and tuberoinfundibular pathways [71, 98]. A nested case-control study using a large-scale claims database in the United States suggested association of some SNRIs and mirtazapine use with EPS [99], and there are several

case reports that SNRIs and tetracyclic antidepressants induce EPS [100–106]. A recent review said that case reports associating serotonergic antidepressants including SSRIs and SNRIs with EPS continued to be published [107]. The results in the present study corresponded with these reports.

Both typical and atypical antipsychotics were significantly associated with EPS, and the ASR of atypical antipsychotics was higher than that of typical ones. Although earlier publications suggested that atypical antipsychotics produced fewer EPS compared with typical ones [108, 109], there are some reports that the risk of EPS is not different between typical and atypical antipsychotics [110, 111]. A large retrospective cohort study of elderly with dementia suggested that the risk of parkinsonism associated with high-dose atypical antipsychotics was similar to that associated with typical ones [89]. Several meta-analyses indicated that low-potency typical antipsychotics might not induce more EPS than atypical ones [112, 113]. Moreover, Japanese studies reported that the signal of EPS was higher in atypical antipsychotics than in typical ones [87, 114]. In the present study, the chlorpromazine-equivalent total daily dose of atypical antipsychotics (216.3 mg/day) was much higher than that of typical ones (76.5 mg/day) at the exposure month. This might be because many atypical antipsychotics have higher potency than typical ones. The results of the present study are consistent with the fact that the risk of antipsychotics-induced EPS increases dose-dependently [89–91].

3.4.2 Hyperlipidemia

In this study, it was suggested that prescription of 2 or more BZs was associated with hyperlipidemia. In the analyses by subclasses of the psychotropic drugs, only SSRIs and atypical antipsychotics were significantly associated with hyperlipidemia. The result in antipsychotics corresponded with previous reports [80, 115]. In addition,

adverse effects such as cholesterol elevation and weight gain are reported in SSRIs in Japanese package inserts although the frequency is not so high (<1%) [116]. A previous report suggested that SSRIs were associated with weight gain in the presence of unhealthy lifestyles [117]. The association between BZs and hyperlipidemia was rarely reported, but some studies using large-scale databases suggested association between insomnia and hyperlipidemia [118, 119]. There was a possibility that unhealthy lifestyle due to insomnia might cause hyperlipidemia. However, if the lifestyle is stable during the evaluation window, its influence is excluded as the reason of the risk elevation.

In this study, no clear and consistent signals were identified for hypertension, diabetes mellitus, pneumonia, bone fracture, and acute myocardial infarction in any drug categories of the psychotropic drugs.

3.4.3 Chapter summary

Some safety events were associated with any drug categories in the psychotropic drugs and whose safety signal was stronger in polypharmacy or high-dose prescription of the psychotropic drugs. On the other hand, the significant signals were identified only in specific subclasses of the psychotropic drugs.

In the Japanese polypharmacy reduction policy for the psychotropic drugs revised in 2016, the reduction rule was applied only to the number of drugs, not to total doses (Table 1). In addition, BZs were separately classified as anxiolytics or hypnotics (Appendix Table 1). The reduction policy should be applied to polypharmacy of BZs since they have similar safety profiles, and the rule considering drug subclasses and total doses in addition to the number of prescribed drugs should be taken into account.

There are some limitations in this study. First, since the insurance claims included a monthly summary of health care services provided by health care providers, date information for prescribing, dispensing, and diagnosis was not available for all cases. Therefore, drugs prescribed at the exposure month for each category of the psychotropic drugs was regarded as a simultaneous prescription. Furthermore, the patients whose initial exposure and outcome occurred in the same month were regarded as a simultaneous occurrence and excluded from calculation of the sequence ratio as previous reports [86, 87]. EPS can be divided into two syndromes: acute syndromes (those that develop generally within hours or days of treatment) and tardive syndromes (those that develop after a sustained period of exposure) [79]. There is a possibility that the present study could not examine the acute syndromes of EPS. On the other hand, antiparkinsonian drugs are sometimes prescribed prophylactically together with antipsychotics [120]; then, for patients who had both prescription in the same month, antiparkinsonian drugs might be prescribed prophylactically, and we might be able to exclude such patients. Second, the elderly aged ≥ 75 years were not included because the claims data used in this study were mainly for those covered by employment-based health insurance. Third, an SSA was conducted by the number of prescribed drugs (1, 2, and 3 or more) for each category of the psychotropic drugs at the exposure month, and the number of prescribed drugs after the exposure month was not considered, since the SSA design could assess only sequence symmetry of the initial prescription of each category of the psychotropic drugs and the initial outcome occurrence. Fourth, this study did not evaluate the effect of time-varying confounders such as age, concomitant drugs other than those of the same subclasses, and the occurrence of acute illness. However, the effect of these confounders was reduced by limiting the interval between the exposure month and the outcome occurrence month up to 12 months [67].

4. Overall discussion and conclusions

In Research 1, the changes in psychotropic prescriptions after the introduction and revisions of the polypharmacy reduction policy were examined using two large-scale Japanese medical databases. The effect of the policy reducing the proportions of patients with 3 or more drugs in anxiolytics, hypnotics, antidepressants, and antipsychotics was identified, but not in BZs. Only limited effects were seen for increasing the proportions of monotherapy and reducing the proportions of patients above clinically recommended doses. Moreover, the proportion of patients with nonpharmacological treatments was much lower than that with psychotropic prescriptions throughout the study period.

In Research 2, some safety events were associated with any drug categories in the psychotropic drugs and whose safety signal was stronger in polypharmacy or high-dose prescription of the psychotropic drugs. On the other hand, the significant signals were identified only in specific subclasses of the psychotropic drugs.

In the polypharmacy reduction policy for the psychotropic drugs, the reduction rule was applied only to the number of drugs, not to total doses. In addition, BZs were separately classified as anxiolytics or hypnotics. Based on our two researches, it was suggested that the rule considering total doses and drug subclasses including BZs in addition to the number of prescribed drugs should be taken into account. In addition, environmental improvement for expanding alternative nonpharmacological treatments such as establishment of their insurance reimbursement and incentive fees as well as nurturing these therapists would be needed. In the future, it is desirable to evaluate the influence of the interventions for psychotropic prescriptions on the true outcomes such as disease improvement or deterioration, rates of adverse events, medical resource utilization, and medical cost.

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Appendix

Appendix Table 1. List of psychotropic drugs

Category	Generic name	Dose equivalence (mg/day)
Anxiolytics	Alprazolam [a]	0.8
	Bromazepam [a]	2.5
	Chlordiazepoxide [a]	10
	Clorazepate dipotassium [a]	7.5
	Clotiazepam [a]	10
	Cloxazolam [a]	1.5
	Diazepam [a]	5
	Ethyl loflazepate [a]	1.67
	Etizolam [a]	1.5
	Fludiazepam [a]	0.5
	Flutazolam [a]	15
	Flutoprazepam [a]	1.67
	Gamma oryzanol	—
	Hydroxyzine hydrochloride	—
	Hydroxyzine pamoate	—
	Lorazepam [a]	1.2
	Medazepam [a]	10
	Mexazolam [a]	1.67
	Oxazolam [a]	20
	Tandospirone citrate	25
	Tofisopam [a]	125
Hypnotics	Amobarbital [b]	50
	Barbital [b]	75
	Bromovalerylurea [b]	500
	Brotizolam [a]	0.25
	Chloral hydrate [b]	250
	Chlorpromazine hydrochloride/ promethazine hydrochloride/ phenobarbital [b]	15
	Estazolam [a]	2
	Eszopiclone [a]	2.5
	Flunitrazepam [a]	1
	Flurazepam hydrochloride [a]	15
	Haloxazolam [a]	5
	Lormetazepam [a]	1
	Nimetazepam [a]	5
	Nitrazepam [a]	5
	Pentobarbital calcium [b]	50
	Phenobarbital [b]	15
	Phenobarbital sodium [b]	15
	Quazepam [a]	15
	Ramelteon	—
	Rilmazafone hydrochloride hydrate [a]	2
	Suvorexant [b]	—
	Triazolam [a]	0.25
	Triclofos sodium [b]	—
	Zolpidem tartrate [a]	10
	Zopiclone [a]	7.5

[a] Benzodiazepine receptor agonist (BZ)
[b] Barbiturate and non-barbiturate (BAR)

Category	Generic name	Dose equivalence (mg/day)
Antidepressants	Amitriptyline hydrochloride [a]	150
	Amoxapine [a]	150
	Clomipramine hydrochloride [a]	120
	Dosulepin hydrochloride [a]	150
	Duloxetine hydrochloride [b]	30
	Escitalopram oxalate [c]	20
	Fluvoxamine maleate [c]	150
	Imipramine hydrochloride [a]	150
	Lofepramine hydrochloride [a]	150
	Maprotiline hydrochloride [d]	150
	Mianserin hydrochloride [d]	60
	Milnacipran hydrochloride [b]	100
	Mirtazapine [d]	30
	Nortriptyline hydrochloride [a]	75
	Paroxetine hydrochloride hydrate [c]	Controlled-release tablet: 50, Other formulation: 40
	Pemoline	—
	Sertraline hydrochloride [c]	100
	Setiptiline maleate [d]	6
	Trazodone hydrochloride	300
	Trimipramine maleate [a]	150
	Venlafaxine hydrochloride [b]	150

[a] Tricyclic antidepressant
[b] Serotonin norepinephrine reuptake inhibitor (SNRI)
[c] Selective serotonin reuptake inhibitor (SSRI)
[d] Tetracyclic antidepressant

Category	Generic name	Dose equivalence (mg/day)
Antipsychotics	Aripiprazole [a]	Oral: 4 mg/day, Long-acting injection: 100 mg/ 4 week
	Blonanserin [a]	4
	Bromperidol [b]	2
	Chlorpromazine hydrochloride [b]	Oral: 100, Intramuscular injection: 33.3
	Chlorpromazine phenolphthalinate [b]	100
	Clocapramine hydrochloride hydrate [b]	40
	Clozapine [a]	50
	Fluphenazine maleate [b]	2
	Fluphenazine decanoate [b]	15 mg/ 4 week
	Haloperidol [b]	Oral: 2, Intramuscular/Intravenous injection: 1
	Haloperidol decanoate [b]	30 mg/ 4 week
	Levomepromazine maleate [b]	Oral: 100, Intramuscular injection: 25
	Mosapramine hydrochloride [b]	33
	Nemonapride [b]	4.5
	Olanzapine [a]	2.5
	Oxypertine [b]	80
	Paliperidone [a]	1.5
	Paliperidone palmitate [a]	18.75 mg/ 4 week
	Perospirone hydrochloride hydrate [a]	8
	Perphenazine [b]	Oral: 10, Intramuscular injection: 2
	Perphenazine fendizoate [b]	10
	Perphenazine maleate [b]	10
	Pimozide [b]	4
	Pipamperone hydrochloride [b]	200
	Prochlorperazine maleate [b]	15
	Propericiazine [b]	20
	Quetiapine fumarate [a]	66
	Reserpine [b]	0.15
	Risperidone [a]	Oral: 1 mg/day, Long-acting injection: 10 mg/ 2 week
	Spiperone [b]	1
	Sulpiride [b]	Oral: 200, Intramuscular injection: 50
	Sultopride hydrochloride [b]	200
	Timiperone [b]	Oral: 1.3, Intramuscular/Intravenous injection: 0.186
	Zotepine [b]	66

[a] Atypical antipsychotic
[b] Typical antipsychotic

Appendix Table 2. Estimated changes of the proportions of patients with 3 or more or 4 or more drugs based on the full segmented regression model

Parameter	Period 1 (Baseline)		Period 2 (Introduction of the policy)		Period 3 (Notification of the revision in 2014)		Period 4 (Enforcement of the revision in 2014)		Period 5 (Revision in 2016)	
	Apr 2011 - Mar 2012		Apr 2012 - Mar 2014		Apr 2014 - Sep 2014		Oct 2014 - Mar 2016		Apr 2016 - Mar 2017	
	Intercept	Baseline trend	Level change	Trend change	Level change	Trend change	Level change	Trend change	Level change	Trend change
Anxiolytics (≥3) (%)	1.8955	-0.2256	-0.1127	0.1512	-0.0810	-0.1173	-0.2731	0.1632	0.0145	-0.0039
	(0.0406)	(0.0738)	(0.0531) *	(0.0797)	(0.0584)	(0.2004)	(0.0709) *	(0.2040)	(0.0529)	(0.0864)
Hypnotics (≥3) (%)	4.8530	0.0137	-0.1183	-0.1160	-0.1962	-2.9928	-0.3706	2.9364	-0.0946	-0.0303
	(0.0784)	(0.1404)	(0.0995)	(0.1536)	(0.1088)	(0.3792) *	(0.1318) *	(0.3888) *	(0.0991)	(0.1692)
Antidepressants (≥3) (%)	4.4553	-0.3168	-0.2456	-0.1140	-0.0828	0.2700	0.2438	0.0180	-1.1622	-0.6144
	(0.0461)	(0.0864)	(0.0630) *	(0.0895)	(0.0773)	(0.2724)	(0.098) *	(0.2736)	(0.0635) *	(0.0951) *
Antidepressants (≥4) (%)	0.6745	0.0223	-0.0934	-0.0786	-0.0065	-0.2964	0.0322	0.2940	-0.0341	-0.1191
	(0.0229)	(0.0414)	(0.0297) *	(0.0449)	(0.0325)	(0.1112) *	(0.0392)	(0.1134) *	(0.0298)	(0.0487) *
Antipsychotics (≥3) (%)	4.9307	0.0110	0.1360	-0.2364	0.2095	-0.5160	-0.0462	0.6072	-0.8227	-1.0908
	(0.0767)	(0.1404)	(0.1013)	(0.1512)	(0.1099)	(0.3780)	(0.1336)	(0.3852)	(0.1023) *	(0.1632) *
Antipsychotics (≥4) (%)	1.1787	-0.0372	0.0191	0.0023	-0.1308	0.2928	-0.1856	-0.3948	-0.1566	0.0032
	(0.0387)	(0.0711)	(0.0514)	(0.0764)	(0.0580) *	(0.1968)	(0.0694) *	(0.1992)	(0.0511) *	(0.0819)
BZs (≥3) (%)	10.3075	-1.2084	-0.0779	1.3968	0.1940	-0.9372	0.0643	0.8160	-0.1788	-0.3408
	(0.2187)	(0.3420)	(0.1506)	(0.4536) *	(0.1524)	(0.8076)	(0.1659)	(0.8268)	(0.1481)	(0.4788)

BZs, benzodiazepine receptor agonists.

Time unit of trend is per year. Values displayed are point estimates (standard errors) for each parameter. The level change parameter and its statistical significance corresponds to the jump between the end of the preceding period and the start of the current period. The trend change parameter and its statistical significance corresponds to the change in trend from the preceding period to the current period. Actual value of the slope in each period is computed by sum of the baseline trend and the cumulative sum of the trends in the previous periods. The periods when the relevant reduction criteria of the polypharmacy reduction policy were introduced or revised are displayed in the gray cells.

* $p < 0.05$

Appendix Table 3. Estimated changes of the proportions of patients above clinically recommended doses and the means of the average daily doses based on the full segmented regression model

Parameter	Period 2 (Introduction of the policy)		Period 3 (Notification of the revision in 2014)		Period 4 (Enforcement of the revision in 2014)		Period 5 (Revision in 2016)	
	Apr 2012 - Mar 2014		Apr 2014 - Sep 2014		Oct 2014 - Mar 2016		Apr 2016 - Mar 2017	
	Intercept	Baseline trend	Level change	Trend change	Level change	Trend change	Level change	Trend change
Proportion of patients above clinically recommended doses								
Sum of anxiolytics and hypnotics	19.6569	-0.5136	0.5582	0.4632	-0.0126	0.1644	0.1130	-0.9384
> 15 mg/day (%) [a]	(0.1593)	(0.0781)	(0.1793) *	(0.6084)	(0.2167)	(0.6180)	(0.1574)	(0.2496) *
BZs > 15 mg/day (%) [a]	18.5554	-0.3768	0.5538	0.1416	0.0512	0.4872	0.0416	-0.7188
	(0.1697)	(0.0832)	(0.1832) *	(0.6144)	(0.2175)	(0.6264)	(0.1621)	(0.2640) *
Antidepressants > 200 mg/day (%) [a]	12.5207	-0.0979	0.0932	0.0120	0.0192	-0.1464	0.0536	0.7788
	(0.0864)	(0.0426)	(0.1240)	(0.4224)	(0.1553)	(0.4284)	(0.1275)	(0.1884) *
Antipsychotics > 450 mg/day (%) [a]	13.4431	-0.9600	0.3145	0.3852	-0.0551	0.6768	-0.0960	-0.9024
	(0.1835)	(0.0897)	(0.1945)	(0.6756)	(0.2404)	(0.6864)	(0.1765)	(0.2880) *
Mean of average daily doses								
Sum of anxiolytics and hypnotics	14.8720	-0.4044	0.2961	-0.0683	-0.2267	0.6624	-0.0838	-0.7092
(mg/day) [b]	(0.1181)	(0.0578)	(0.1341) *	(0.4608)	(0.1643)	(0.4668)	(0.1181)	(0.1860) *
BZs (mg/day) [b]	14.4379	-0.3660	0.3262	-0.2616	-0.1647	0.8988	-0.1393	-0.4776
	(0.1140)	(0.0558)	(0.1294) *	(0.4440)	(0.1583)	(0.4500)	(0.1139)	(0.1800) *
Antidepressants (mg/day) [b]	109.1213	1.0764	0.1675	-2.8824	0.2993	1.1376	0.3241	1.1268
	(0.4081)	(0.1548)	(0.3206)	(1.1316) *	(0.4053)	(1.1316)	(0.3714)	(0.5496) *
Antipsychotics (mg/day) [b]	233.4864	-10.3416	3.7325	2.8464	-0.1536	8.7852	-3.4511	-13.0284
	(3.1468)	(1.5456)	(3.4080)	(11.5656)	(4.0617)	(11.8116)	(3.0804)	(4.9932) *

BZ, benzodiazepine receptor agonists.

Time unit of trend is per year. Diazepam-equivalent doses for anxiolytics and hypnotics as well as BZs, imipramine-equivalent doses for antidepressants, and chlorpromazine-equivalent doses for antipsychotics were used. The level change parameter and its statistical significance corresponds to the jump between the end of the preceding period and the start of the current period. The trend change parameter and its statistical significance corresponds to the change in trend from the preceding period to the current period. Actual value of the slope in each period is computed by sum of the baseline trend and the cumulative sum of the trends in the previous periods.

[a] Proportion of patients prescribed with more than clinically recommended doses in Japan. Values displayed are point estimates (standard errors) of each parameter.

[b] Mean of the average daily doses. Values displayed are point estimates (standard errors) of each parameter.

* $p < 0.05$

Appendix Table 4. Outcome definition

Disease	ICD-10 code	Therapeutic drug name
Hypertension	I10, I11, I12, I13, I15	Acebutolol hydrochloride
		Alacepril
		Aliskiren fumarate
		Amlodipine besylate
		Amlodipine besylate/ atorvastatin calcium hydrate
		Amosulalol hydrochloride
		Aranidipine
		Arotinolol hydrochloride
		Atenolol
		Azelnidipine
		Azilsartan
		Azilsartan/ amlodipine besylate
		Barnidipine hydrochloride
		Benazepril hydrochloride
		Benidipine hydrochloride
		Bentylhydrochlorothiazide
		Benzylhydrochlorothiazide/ reserpine/ carbazochrome
		Betaxolol hydrochloride
		Bevantolol hydrochloride
		Bisoprolol fumarate
		Bunazosin hydrochloride
		Candesartan cilexetil
		Candesartan cilexetil/ amlodipine besylate
		Candesartan cilexetil/ hydrochlorothiazide
		Captopril
		Carteolol hydrochloride
		Carvedilol
		Celiprolol hydrochloride
		Cilazapril hydrate
		Cilnidipine
		Clonidine hydrochloride
		Delapril hydrochloride
		Diltiazem hydrochloride
		Doxazosin mesilate
		Efonidipine hydrochloride ethanolate
		Enalapril maleate
		Eplerenone
		Felodipine
		Furosemide
		Guanabenz acetate
		Hydralazine hydrochloride
		Hydrochlorothiazide
		Imidapril hydrochloride
		Indapamide
		Irbesartan
		Irbesartan/ amlodipine besylate
		Irbesartan/ trichlormethiazide
		Labetalol hydrochloride
		Lisinopril hydrate
		Losartan potassium
		Losartan potassium/ hydrochlorothiazide
		Manidipine hydrochloride
		Mefruside

Disease	ICD-10 code	Therapeutic drug name
		Methyldopa hydrate
		Meticrane
		Metoprolol tartrate
		Nadolol
		Nicardipine hydrochloride
		Nifedipine
		Nilvadipine
		Nipradilol
		Nisoldipine
		Nitrendipine
		Olmesartan medoxomil
		Olmesartan medoxomil/ azelnidipine
		Perindopril erbumine
		Pindolol
		Prazosin hydrochloride
		Propranolol hydrochloride
		Quinapril hydrochloride
		Reserpine
		Spironolactone
		Telmisartan
		Telmisartan/ amlodipine besylate
		Telmisartan/ hydrochlorothiazide
		Temocapril hydrochloride
		Terazosin hydrochloride hydrate
		Trandolapril
		Triamterene
		Trichlormethiazide
		Tripamide
		Urapidil
		Valsartan
		Valsartan/ amlodipine besylate
		Valsartan/ cilnidipine
		Valsartan/ hydrochlorothiazide
Diabetes mellitus	E10, E11, E13, E14, R73	Acarbose
		Acetohexamide
		Alogliptin benzoate
		Alogliptin benzoate/ pioglitazone hydrochloride
		Amorphous insulin zinc
		Anagliptin
		Buformin hydrochloride
		Canagliflozin hydrate
		Chlorpropamide
		Crystalline insulin zinc
		Dapagliflozin propylene glycolate hydrate
		Dulaglutide (genetic modification)
		Empagliflozin
		Exenatide
		Glibenclamide
		Gliclazide
		Glimepiride
		Glyclopyramide
		Human insulin (genetic modification)
		Insulin
		Insulin aspart (genetic modification)
		Insulin degludec (genetic modification)
		Insulin degludec (genetic modification)/ insulin aspart (genetic

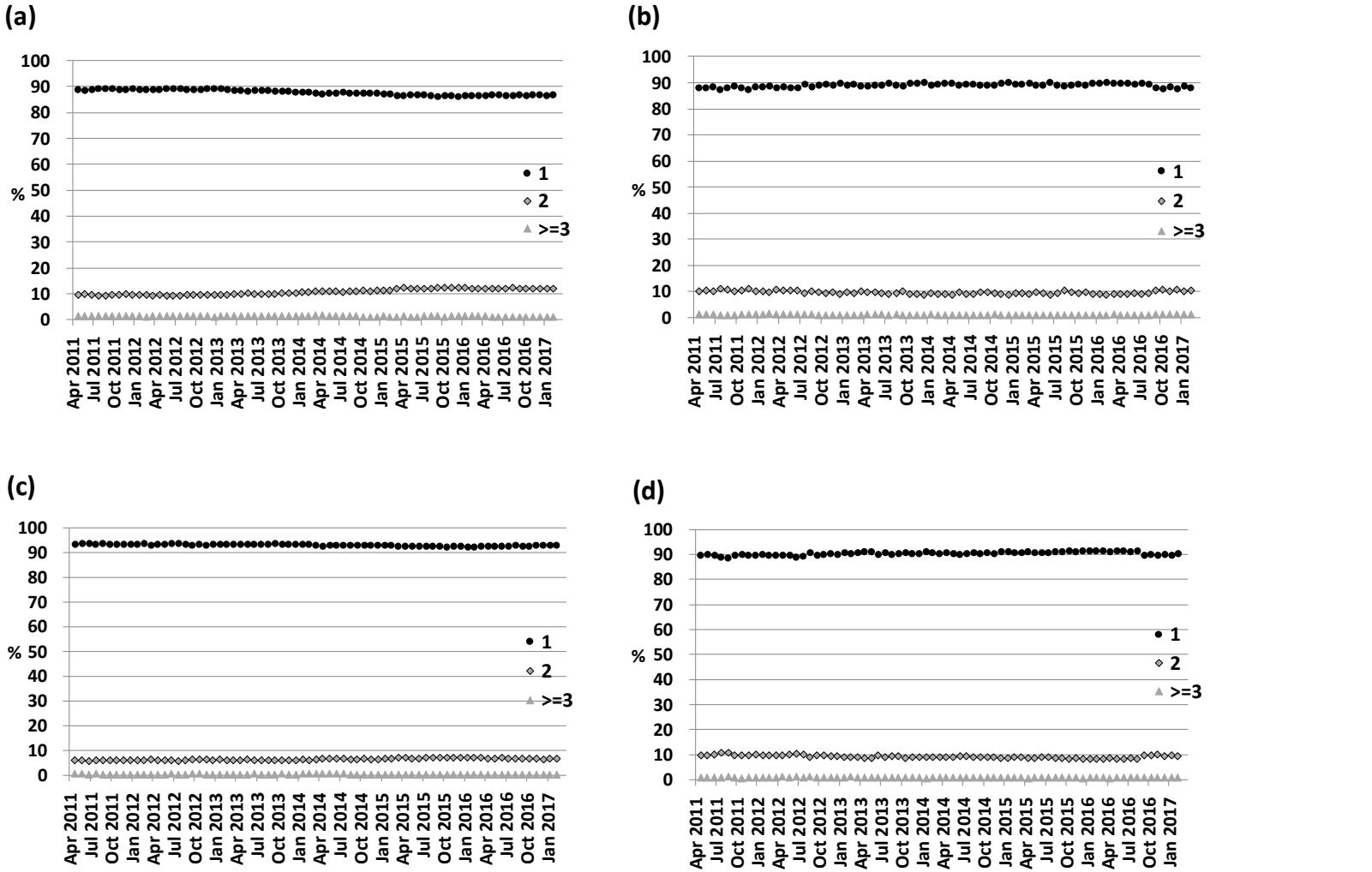
Disease	ICD-10 code	Therapeutic drug name
		modification)
		Insulin detemir (genetic modification)
		Insulin glargine (genetic modification)
		Insulin glulisine (genetic modification)
		Insulin glargine (genetic modification) [successor 1]
		Insulin lispro (genetic modification)
		Insulin zinc
		Ipragliflozin L-proline
		Isophane insulin
		Linagliptin
		Liraglutide (genetic modification)
		Lixisenatide
		Luseogliflozin hydrate
		Metformin hydrochloride
		Miglitol
		Mitiglinide calcium hydrate
		Mitiglinide calcium hydrate/ voglibose
		Nateglinide
		Omarigliptin
		Pioglitazone hydrochloride
		Pioglitazone hydrochloride/ glimepiride
		Pioglitazone hydrochloride/ metformin hydrochloride
		Protamine zinc insulin
		Repaglinide
		Saxagliptin hydrate
		Sitagliptin phosphate hydrate
		Teneligliptin hydrobromide hydrate
		Tofogliflozin hydrate
		Tolbutamide
		Trelagliptin succinate
		Vildagliptin
		Vildagliptin/ metformin hydrochloride
		Voglibose
Pneumonia	J10.0, J11.0, J12-J18, J22	Amikacin sulfate
		Amoxicillin hydrate
		Ampicillin hydrate
		Ampicillin hydrate/ cloxacillin sodium hydrate
		Ampicillin sodium/ cloxacillin sodium hydrate
		Ampicillin sodium/ sulbactam sodium
		Arbekacin sulfate
		Atovaquone
		Azithromycin hydrate
		Aztreonam
		Bacampicillin hydrochloride
		Benzylpenicillin benzathine hydrate
		Benzylpenicillin potassium
		Biapenem
		Cefaclor
		Cefazolin sodium
		Cefcapene pivoxil hydrochloride hydrate
		Cefdinir
		Cefditoren pivoxil
		Cefepime hydrochloride hydrate
		Cefixime hydrate
		Cefmenoxime hydrochloride
		Cefmetazole sodium

Disease	ICD-10 code	Therapeutic drug name
		Cefminox sodium hydrate
		Cefoperazone sodium
		Cefotaxime sodium
		Cefotiam hexetil hydrochloride
		Cefotiam hydrochloride
		Cefozopran hydrochloride
		Cefpirome sulfate
		Cefpodoxime proxetil
		Ceftazidime hydrate
		Cefteram pivoxil
		Ceftizoxime sodium
		Ceftriaxone sodium hydrate
		Cephalexin
		Cephalothin sodium
		Chloramphenicol
		Chloramphenicol sodium succinate
		Ciprofloxacin
		Ciprofloxacin hydrochloride
		Clarithromycin
		Clindamycin hydrochloride
		Clindamycin phosphate
		Colistin sodium methanesulfonate
		Demethylchlortetracycline hydrochloride
		Dibekacin sulfate
		Doxycycline hydrochloride hydrate
		Erythromycin
		Erythromycin ethylsuccinate
		Erythromycin lactobionate
		Erythromycin stearate
		Faropenem sodium hydrate
		Fosfomycin sodium
		Garenoxacin mesilate hydrate
		Gentamicin sulfate
		Imipenem hydrate/ cilastatin sodium
		Isepamicin sulfate
		Josamycin
		Josamycin propionate
		Kanamycin sulfate salt
		Latamoxef sodium
		Levofloxacin hydrate
		Lincomycin hydrochloride
		Linezolid
		Lomefloxacin hydrochloride
		Meropenem hydrate
		Minocycline hydrochloride
		Moxifloxacin hydrochloride
		Ofloxacin
		Panipenem/ betamipron
		Pazufloxacin mesilate
		Piperacillin sodium
		Prulifloxacin
		Quinupristin/ dalfopristin
		Ribostamycin sulfate
		Roxithromycin
		Sitafloxacin hydrate
		Spiramycin acetate

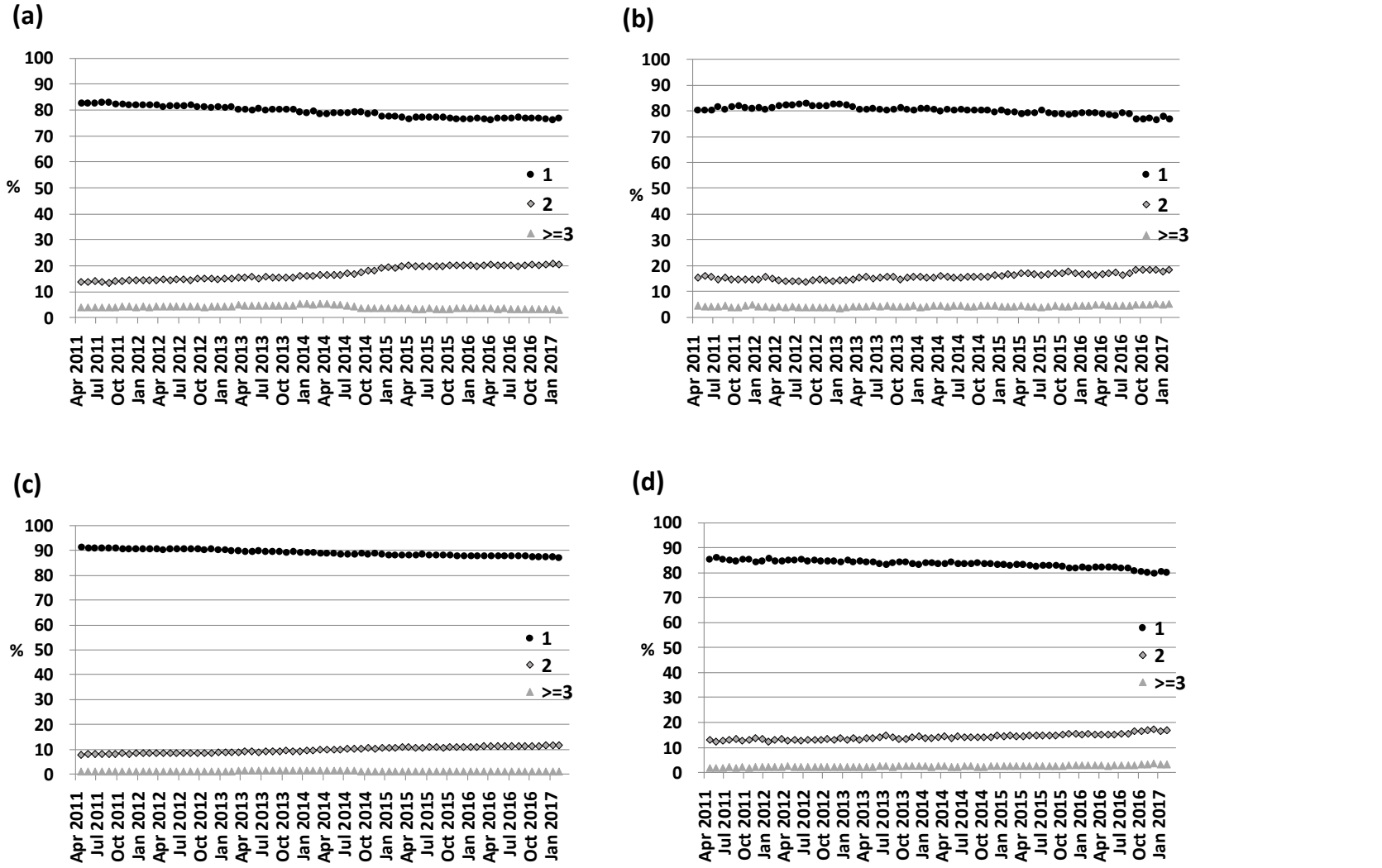
Disease	ICD-10 code	Therapeutic drug name
		Sulbactam sodium/ cefoperazone sodium
		Sulfamethoxazole-trimethoprim
		Sultamicillin tosilate hydrate
		Tazobactam sodium/ piperacillin sodium
		Tebipenemu pivoxil
		Teicoplanin
		Tetracycline hydrochloride
		Tobramycin
		Tosufloxacin tosilate hydrate
		Vancomycin hydrochloride
EPS	G20-G26	Amantadine hydrochloride
		Apomorphine hydrochloride hydrate
		Biperiden hydrochloride
		Bromocriptine mesylate
		Cabergoline
		Droxidopa
		Entacapone
		Istradefylline
		Levodopa
		Levodopa/ benserazide hydrochloride
		Levodopa/ carbidopa hydrate
		Levodopa/ carbidopa hydrate/ entacapone
		Mazaticol hydrochloride
		Pergolide mesylate
		Pirohepuchin hydrochloride
		Pramipexole hydrochloride hydrate
		Profenamine hibenzate
		Profenamine hydrochloride
		Ropinirole hydrochloride
		Rotigotine
		Selegiline hydrochloride
		Talipexole hydrochloride
		Trihexyphenidyl hydrochloride
		Zonisamide
Hyperlipidemia	E78.0-E78.5	Amlodipine besilate/ atorvastatin calcium hydrate (1)
		Amlodipine besilate/ atorvastatin calcium hydrate (2)
		Amlodipine besilate/ atorvastatin calcium hydrate (3)
		Amlodipine besilate/ atorvastatin calcium hydrate (4)
		Atorvastatin calcium hydrate
		Bezafibrate
		Cholestyramine
		Clinofibrate
		Clofibrate
		Colestimide
		Dextran sulfate sodium
		Elastase
		Ethyl icosapentate
		Ezetimibe
		Fenofibrate
		Fluvastatin sodium
		Niceritrol
		Nicomol
		Omega-3-acid ethyl esters
		Pitavastatin calcium
		Polyenephosphatidylcholine

Disease	ICD-10 code	Therapeutic drug name
		Pravastatin sodium Probucol Rosuvastatin calcium Simvastatin

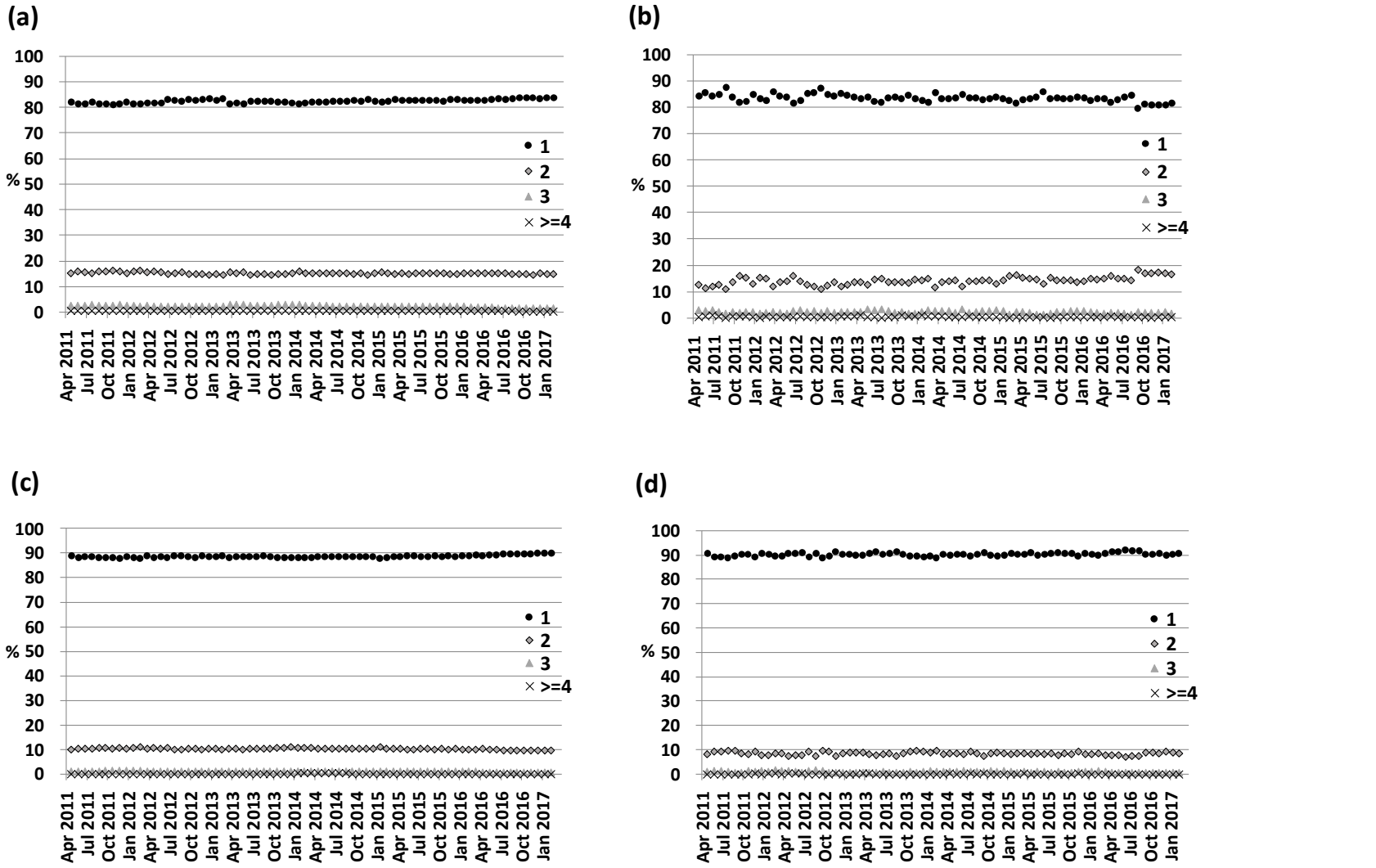
Disease	ICD-10 code	Medical procedure code (system code for processing claims)
Bone fracture	M48.4, M48.5, S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T14.2	150016510, 150016610, 150016710, 150016810, 150016910, 150017010, 150017110, 150017210, 150017310, 150017450, 150017550, 150017650, 150018110, 150018210, 150018310, 150018410, 150018510, 150018610, 150018710, 150018810, 150018910, 150019010, 150019110, 150019210, 150019310, 150019410, 150019510, 150019610, 150019710, 150019810, 150029610, 150029710, 150029810, 150029910, 150030010, 150030110, 150030210, 150030310, 150030410, 150042610, 150042710, 150042810, 150042910, 150043010, 150043110, 150043210, 150043310, 150043410, 150060410, 150060810, 150060910, 150081310, 150097710, 150097950, 150098010, 150098110, 150114510, 150114610, 150114710, 150115010, 150115110, 150115210, 150123010, 150242910, 150261010, 150261110, 150261810, 150274210, 150274310, 150274410, 150284110, 150289110, 150289210, 150289910, 150294810, 150295410, 150296210, 150334110, 150345610, 150345710, 150352010, 150352110, 150352210, 150352310, 150352410, 150352510, 150352610, 150352710, 150353210, 150353310, 150353410, 150353510, 150353610, 150353710, 150353810, 150353910, 150354010, 150356610, 150370370, 150384510
Acute myocardial infarction	I21	150284310, 150359310, 150374910, 150375210



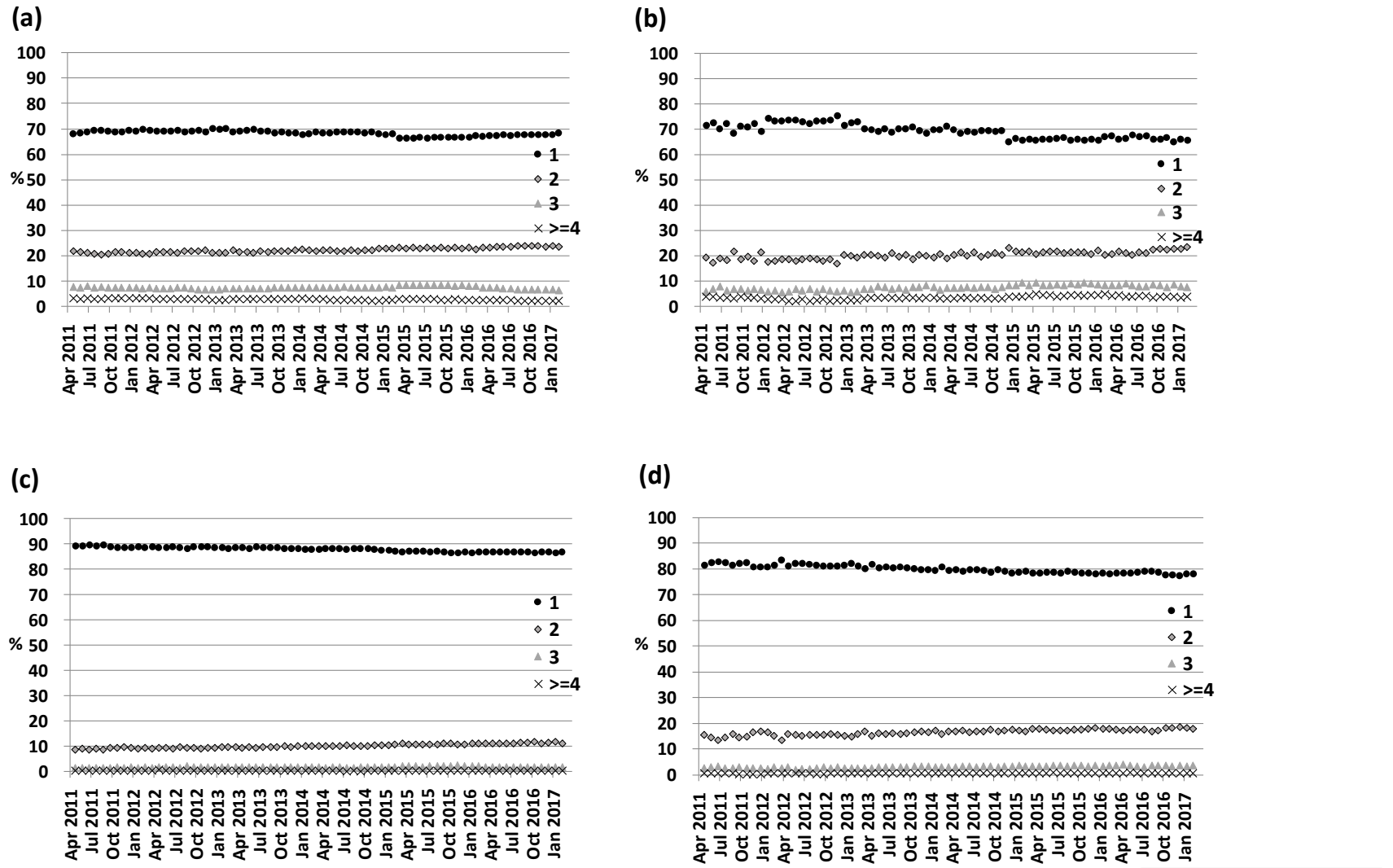
Appendix Figure 1-1. Observed changes of the proportions of patients by the number of prescribed drugs: Anxiolytic



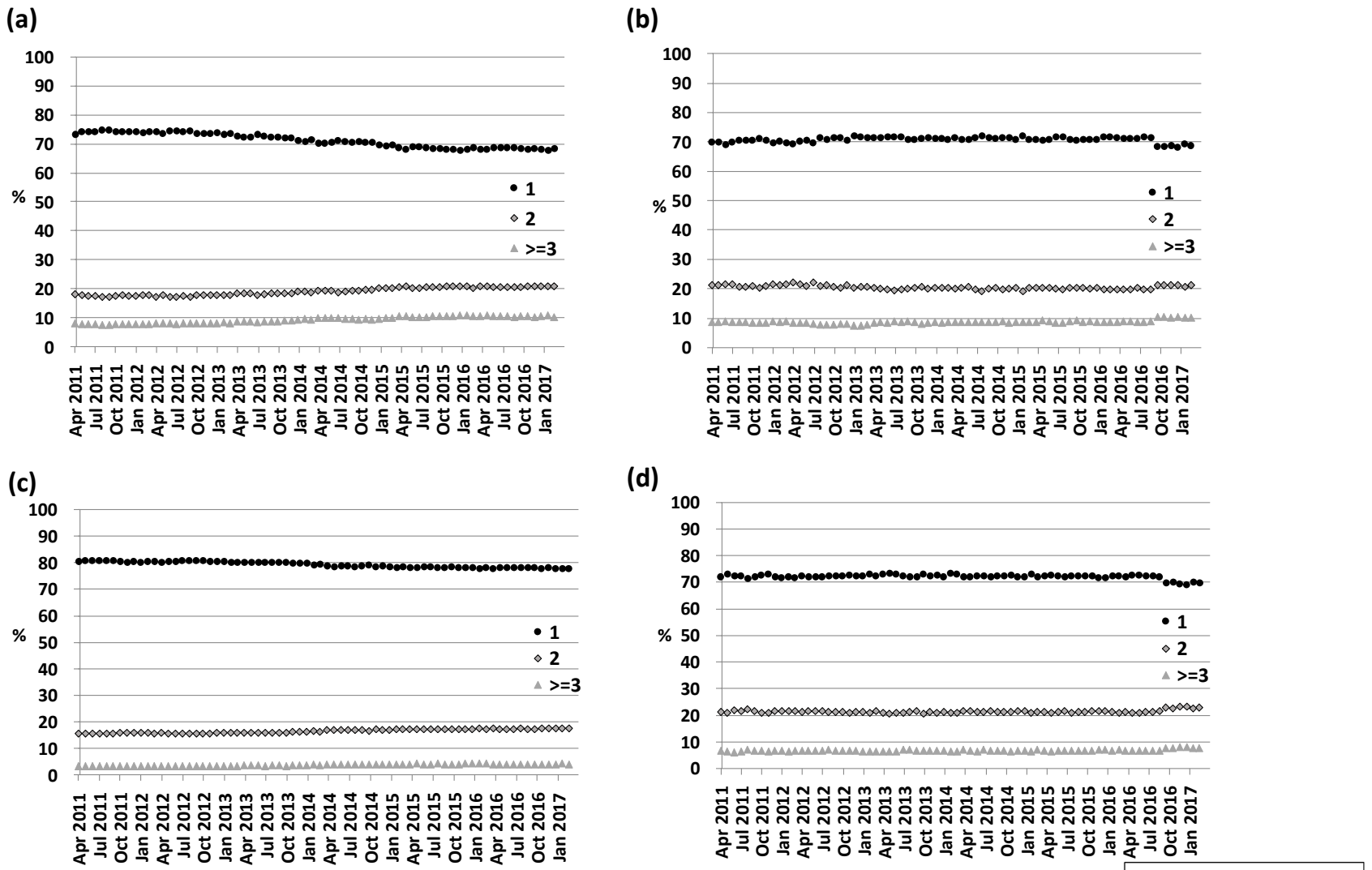
Appendix Figure 1-2. Observed changes of the proportions of patients by the number of prescribed drugs: Hypnotics



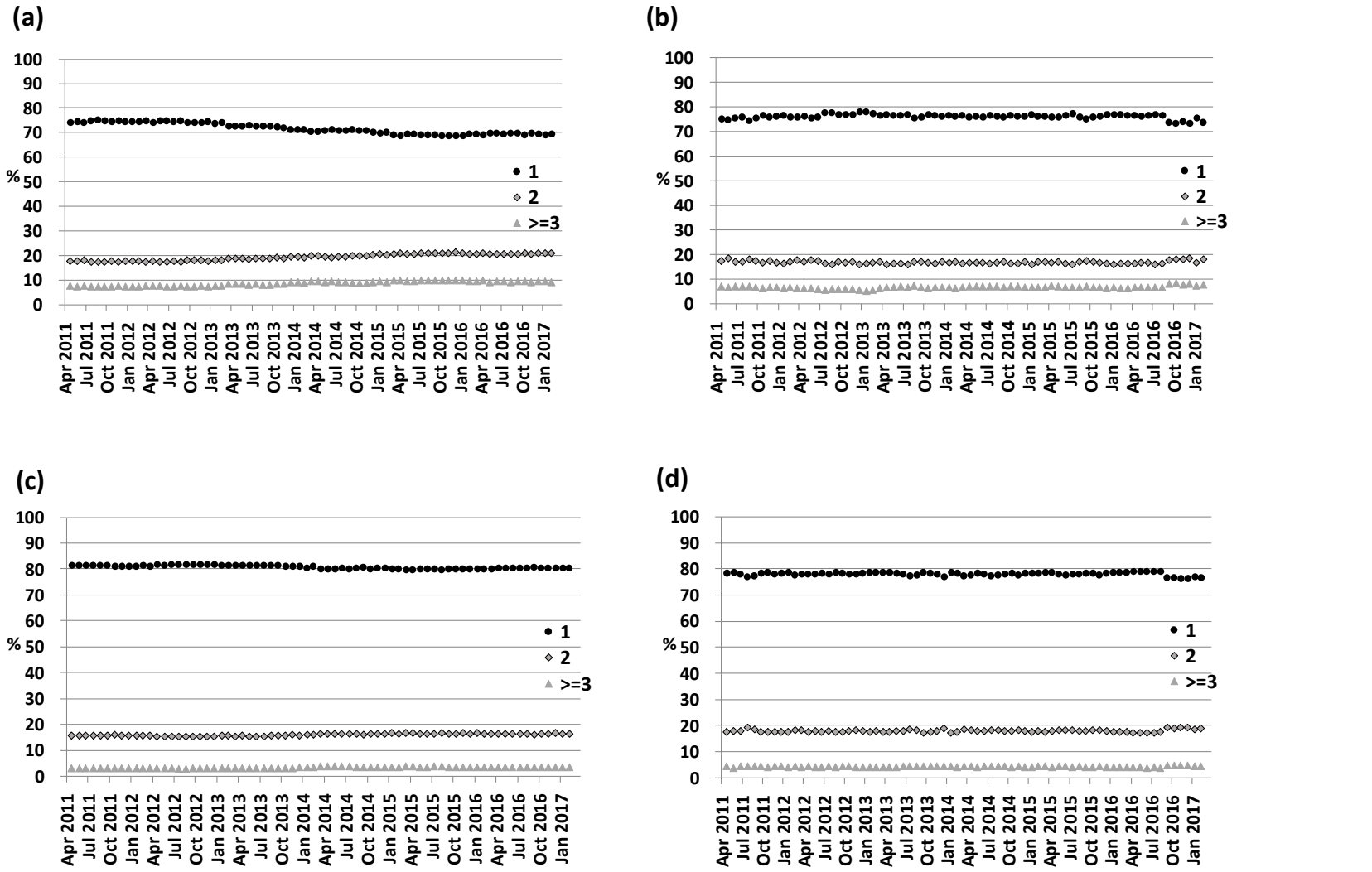
Appendix Figure 1-3. Observed changes of the proportions of patients by the number of prescribed drugs: Antidepressants



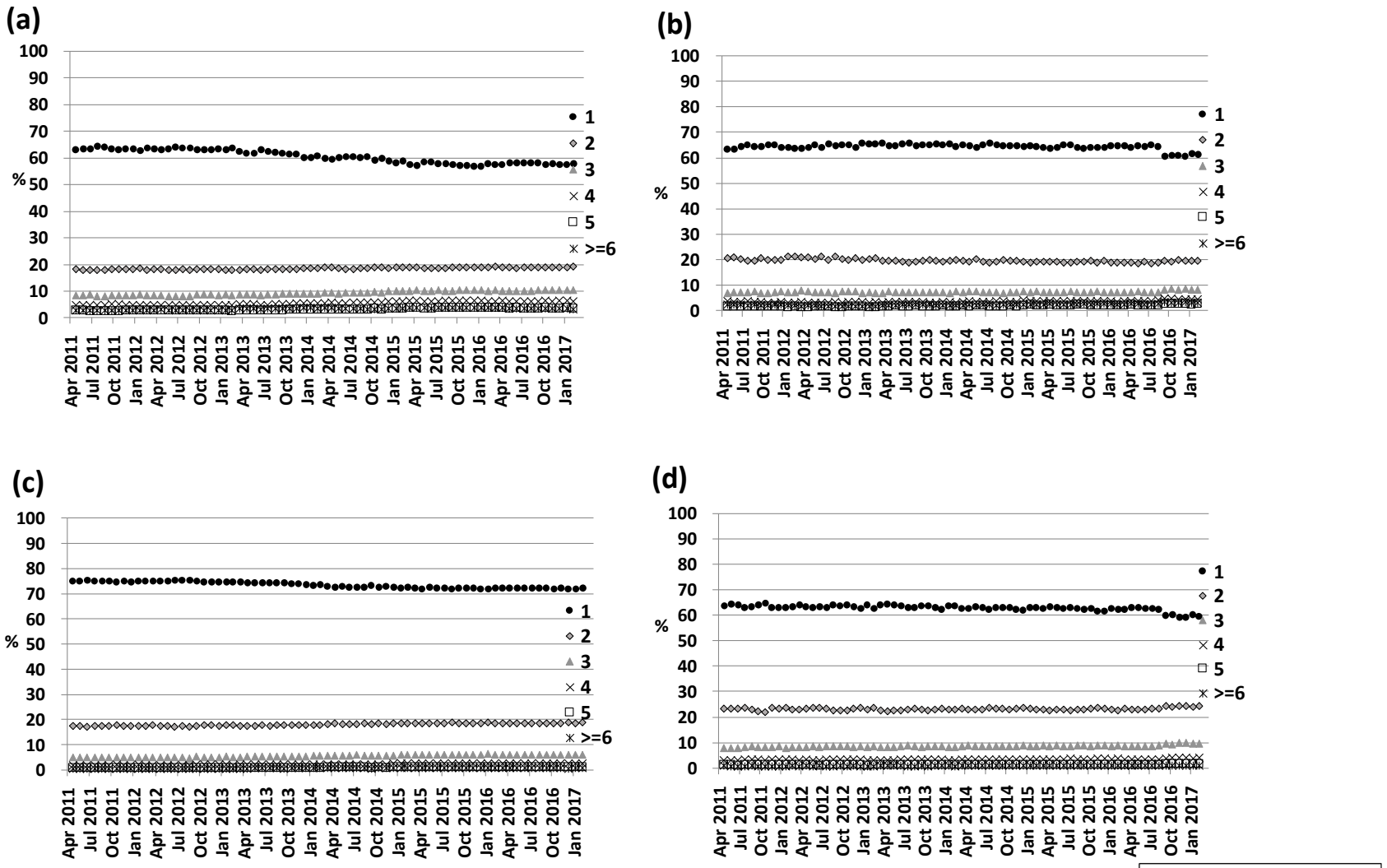
Appendix Figure 1-4. Observed changes of the proportions of patients by the number of prescribed drugs: Antipsychotics



Appendix Figure 1-5. Observed changes of the proportions of patients by the number of prescribed drugs: Sum of anxiolytics and hypnotics



Appendix Figure 1-6. Observed changes of the proportions of patients by the number of prescribed drugs: BZs BZ, benzodiazepine receptor agonist.



Appendix Figure 1-7. Observed changes of the proportions of patients by the number of prescribed drugs: Sum of psychotropic drugs sum of psychotropic drugs, sum of anxiolytics, hypnotics, antidepressants, and antipsychotics.