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Characteristics of discharge prescriptions for patients with schizophrenia or major depressive disorder: Real-world evidence from the Effectiveness of Guidelines for Dissemination and Education (EGUIDE) psychiatric treatment project

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ABSTRACT

Background: Monopharmacy with antipsychotics and antidepressants is the first-line treatment for schizophrenia and major depressive disorder (MDD) in most clinical guidelines, while polypharmacy with psychotropic agents in the treatment of schizophrenia is common in clinical practice. There are no detailed data on the prescription patterns for inpatients with mental illness with reliable diagnoses made by treating psychiatrists.

Methods: We gathered prescription data at discharge from 2177 patients with schizophrenia and 1238 patients with MDD from October 2016 to March 2018.

Results: The patients with schizophrenia aged between 60 and 79 were prescribed lower doses of antipsychotics and hypnotics/anxiolytics than those aged between 40 and 59. There were significant differences between the prescription rate of antipsychotics in the patients with schizophrenia and that of antidepressants in the patients with MDD. The frequency of concomitant drugs such as anti-Parkinson drugs, anxiolytics/hypnotics and mood

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stabilizers in the subjects with schizophrenia prescribed antipsychotic polypharmacy was significantly higher than that with monotherapy. For the patients with schizophrenia, olanzapine, risperidone, aripiprazole, quetiapine, and blonanserin were the five most prescribed antipsychotics. For the patients with MDD, mirtazapine, duloxetine, escitalopram, trazodone and sertraline were the five most prescribed antidepressants.
Conclusions: Our results showed the use of high doses of antipsychotics, high percentages of antipsychotic polypharmacy and concurrent use of hypnotics/anxiolytics in patients with schizophrenia. Notably, these data were collected before intensive instruction regarding the guidelines; therefore, we need to assess the change in the prescription pattern post guideline instruction.

1. Introduction

To date, antipsychotics remain a mainstay for treating schizophrenia. Second-generation antipsychotic monotherapy with no or a few exceptional concurrent uses of other psychotropics is recommended in most guidelines (Association, 2020; Buchanan et al., 2010; Neuropsychopharmacology, 2016). However, both concurrent prescription of two or more antipsychotics (antipsychotic polypharmacy) and concurrent use of psychotropic agents in the treatment of schizophrenia is common in clinical practice (Leslie and Rosenheck, 2004; Yang et al., 2018). Two recent studies showed a decrease in antipsychotic polypharmacy in Japan, although they were based on outpatient data; additionally, one of the studies lacked reliable diagnostic data (Kochi et al., 2017), and the other lacked data on other psychotropics (Hata et al., 2020). Regarding inpatient prescription data, the 4th Research on Asian Psychotropic Prescription Pattern (REAP) project showed that more than half of the subjects received antipsychotic polypharmacy and concomitant use of hypnotics in inpatient settings in Japan, although the number of subjects was not large (Yang et al., 2018). Thus, we need prescription information about inpatient pharmacotherapy, which includes psychotropics other than antipsychotics, for a large number of patients with schizophrenia.

Antidepressants are the first-line treatment for major depressive disorder (MDD) in most clinical guidelines (Bauer et al., 2017; Hillhouse and Porter, 2015). When selecting an antidepressant, there are two main considerations: efficacy and tolerability. The psychopharmacotherapy of MDD can be simple, with the use of only one antidepressant controlling symptoms in most cases. However, over the past decades, MDD has also been characterized by an increasing tendency for the use of multiple drugs, not only in geriatric populations but also in adults and the young, e.g., antidepressants and antipsychotics or anxiolytics (Goodwin et al., 2009; McIntyre and Jerrell, 2009; Mojtabai and Olfson, 2010; Serna et al., 2010). In addition, it is recommended in textbooks that for the treatment of treatment-resistant MDD, a combination of two antidepressants (antidepressant polypharmacy) with different pharmacological profiles should be used, and this strategy has shown good results (Stahl, 2013).

In Japan, the Effectiveness of Guidelines for Dissemination and Education (EGUIDE) psychiatric treatment project was launched in 2016. The aims of the EGUIDE project were to disseminate the guidelines that present the treatments for schizophrenia and major depressive disorder via education programs for psychiatrists. In addition, we investigated the effectiveness of the guideline education programs by evaluating the participants' clinical knowledge regarding the guidelines before and after the programs. In the EGUIDE project, we developed a two-day education course for psychiatrists to learn the Japanese treatment guidelines for schizophrenia and MDD (one day for each disorder) (Takaesu et al., 2019). In addition, we investigated the effectiveness of the guideline education programs by evaluating the participants' prescriptions (prescription at discharge of patients with moderate to severe schizophrenia or MDD). In the EGUIDE study, interinstitutional variabilities were found for antipsychotic polypharmacy in schizophrenia and antidepressant polypharmacy in MDD (Ichihashi et al., 2020; Iida et al., 2020). However, there was no real-world individual prescription pattern of psychotropic agents such as antipsychotics and antidepressants.

This study examined the differences in the prescription rates of psychotropic drugs between men and women and the differences in age groups in more detail and investigated prescribed combinations of psychotropic drugs and antipsychotics for schizophrenia or antidepressants for MDDs. We also examined the rate and prescription ranking of individual drugs for each psychotropic drug category.

2. Method

Psychiatrists were recruited from October 2016 to March 2018. Written informed consent was obtained from all participants after the procedures had been fully explained by a chief researcher at the facility (Takaesu et al., 2019). This study was approved by the ethics committees of the National Center of Neurology and Psychiatry (A2017-105) and each participating university/hospital/clinic. The study procedures were conducted according to the Declaration of Helsinki. The protocol of this study was registered in the University Hospital Medical Information Network registry (UMIN000022645).

From 2016 to 2018, prescriptions at discharge at each participating institution from April to September in each year were gathered from participants attending the course using a standardized data collection method that involved participants checking their medical records and manually entering them into an Excel sheet, followed by double-checking by the data manager. We checked the types and dosages of all psychotropic drugs, including antipsychotics, antidepressants, anti-Parkinson agents, hypnotics and anxiolytics, mood stabilizers, and other types of drugs, such as psychostimulants or antidementia agents. Sulpiride and clonazepam were defined as antipsychotics, hypnotics and anxiolytics, respectively. Vegetamin A (chlorpromazine 25 mg, promethazine 12.5 mg and phenobarbital 40 mg) and Vegetamin B (chlorpromazine 12.5 mg, promethazine 12.5 mg and phenobarbital 30 mg) were used as hypnotics and anxiolytics. Acetazolamide and acetylpheneturide were used as mood stabilizers and anticonvalsants. Acamprosate calcium, atomoxetine hydrochloride, cyanamide, disulfiram, donepezil, galantamine, guanfacine, lisdexamfetamine mesylate, memantine, methamphetamine, methylphenidate hydrochloride, methylphenidate hydrochloride (Concerta), modafinil, nalmefene, pemoline, phenobarbital 15 (Trancolon P), phenobarbital 20 (Asthmolysin), and rivastigmine skin patches were regarded as others (see Supplementary Table 1).

Data gathering was conducted from October to December in each year by the EGUIDE project members. Prescription data of 2177 patients who had been diagnosed with schizophrenia and prescription data of 1238 patients who had been diagnosed with MDDs were gathered from 83 institutions (37 university hospitals, 22 national/public hospitals, and 24 private hospitals). We used the first prescription data from each institution only to evaluate the prescription patterns before special intensive and comprehensive instruction about guidelines.

Conventionally, a chlorpromazine equivalent for antipsychotics, imipramine equivalent for antidepressants, benztropine equivalent for anti-parkinson agents, and diazepam/nitrazepam equivalent for hypnotics and anxiolytics are used to sum and compare the daily doses of agents belonging to the same category. Drugs for which no equivalent doses were set were excluded from this type of analysis. The equivalent

doses were calculated based on the study by Inada and Inagaki (Inada and Inagaki, 2015), except for several new agents (Hayasaka et al., 2015; Inagaki and Inada, 2015, 2017; Taylor et al., 2018) (see Supplementary Table 1).

We compared the percentage of prescribed subjects, daily dose, and number of drugs in the prescribed subjects in each category between sexes, between mono- and polypharmacy, and between age groups (0–19, 20–39, 40–59, 60–79, and 80-). The chi-square test was used for categorical variables, and the Wilcoxon rank–sum test (for comparison between sexes or mono- versus polypharmacy) or the Kruskal-Wallis test with Dunn-Bonferroni test (for age groups) was used for continuous and ordered variables. A p-value of <0.05 (two tailed) was considered statistically significant, and Bonferroni correction was applied for multiple comparisons. Because we implemented the same type of analysis 48 times for each group through this study, $p < 0.001$ (0.05/48) was judged to be significant. Regarding the comparison of the percentage of patients with schizophrenia prescribed antipsychotics and those with MDD prescribed antidepressants in the 5 age groups, the chi-square test was used, and Bonferroni's correction was applied for multiple comparisons in which $p < 0.01$ (0.05/5) was judged to be significant.

3. Results

3.1. Comparison between sexes

As shown in Table 1, prescriptions on discharge of 2177 subjects with schizophrenia were used for the analysis. Female subjects accounted for 54.7 % of the patients with schizophrenia and 65 % of the patients with MDD and were slightly older than male subjects for both schizophrenia and MDD.

Overall, 96.6 % of the subjects with schizophrenia received a prescription for antipsychotics, and the mean number of antipsychotics was 1.6 ± 0.8 (mean ± S.D.), with the chlorpromazine equivalent daily dose of 683.8 ± 451.1 mg/day. Regarding other psychotropics, 30.1 % of the

Table 1
Demographic background and prescription of psychotropics (analysis for sex).

	Schizophrenia				Major Depression Disorder			
	Total	Male	Female	p value	Total	Male	Female	p value
N (male)	2177	986	1191	–	1238	433	805	
age	46 (15.4)	44.7 (14.6)	47.1 (15.9)	0.0002*5,§	58 (17.9)	55.3 (17)	59.4 (18.2)	p = 0.0001*6,§
antipsychotics (%)	96.6	97.2	96.1	0.2333*6	53	50.6	54.3	p = 0.2352*6
mean number of antipsychotics	N = 2103, 1.6 (0.8)	N = 958, 1.6 (0.8)	N = 1145, 1.5 (0.7)	0.0043*7	N = 656, 1.1 (0.3)	N = 219, 1.1 (0.3)	N = 437, 1.1 (0.3)	p = 0.7958*7
mean dose of antipsychotics (mg/day)*1	N = 2100, 683.8 (451.1)	N = 957, 739.6 (470.5)	N = 1143, 637.2 (428.6)	<0.0001*7,§	N = 626, 179.9 (185.7)	N = 209, 184.4 (220.5)	N = 417, 177.7 (165.5)	p = 0.88*7
typical antipsychotics (%)	26.6	28.5	24.9	0.0681*6	9.4	9	9.6	p = 0.8265*6
mean number of typical antipsychotics	N = 578, 1.2 (0.5)	N = 281, 1.3 (0.5)	N = 297, 1.2 (0.4)	0.1272*7	N = 116, 1 (0.2)	N = 39, 1 (0.2)	N = 77, 1.1 (0.2)	p = 0.517*7
mean dose of typical antipsychotics (mg/day)*1	N = 574, 264.9 (309.6)	N = 285, 279.2 (315.9)	N = 289, 250.7 (302.6)	0.0085*7	N = 79, 51.7 (64.6)	N = 27, 32.3 (37.2)	N = 52, 61.7 (73)	p = 0.48*7
atypical antipsychotic drugs (%)	90.1	89.8	90.4	0.6522*6	46	43.9	47.1	p = 0.3087*6
mean number of atypical antipsychotics	N = 1962, 1.3 (0.6)	N = 885, 1.4 (0.6)	N = 1077, 1.3 (0.5)	0.0045*7	N = 569, 1.1 (0.3)	N = 190, 1.1 (0.3)	N = 379, 1.1 (0.3)	p = 0.9046*7
mean dose of atypical antipsychotics (mg/day)*1	N = 1962, 654.5 (407.2)	N = 885, 709.8 (420.8)	N = 1077, 609 (389.8)	<0.0001*7,§	N = 569, 190.8 (184.6)	N = 190, 198.3 (215.8)	N = 379, 187 (166.6)	p = 0.4794*7
anti-Parkinson drugs (%)	30.1	31	29.3	0.4066*6	4.9	3.2	5.8	p = 0.0599*6
mean number of anti-Parkinson drugs	N = 655, 1.1 (0.3)	N = 306, 1.1 (0.3)	N = 349, 1.1 (0.2)	0.1203*7	N = 61, 1.1 (0.3)	N = 14, 1.1 (0.3)	N = 47, 1.1 (0.2)	p = 0.3574*7
mean dose of anti-Parkinson drugs (mg/day)*2	N = 641, 2.6 (1.5)	N = 301, 2.7 (1.5)	N = 340, 2.5 (1.6)	0.0316*7	N = 48, 1.9 (1.1)	N = 11, 1.5 (0.5)	N = 37, 2 (1.2)	p = 0.2004*7
antidepressants (%)	9.2	7.9	10.2	0.0717*6	84.2	82.4	85.2	p = 0.2326*6
mean number of antidepressants	N = 200, 1.1 (0.3)	N = 78, 1.1 (0.3)	N = 122, 1.1 (0.4)	0.3648*7	N = 1043, 1.3 (0.6)	N = 357, 1.3 (0.6)	N = 686, 1.3 (0.6)	p = 0.8086*7
mean dose of antidepressants (mg/day)*3	N = 186, 90.4 (83.3)	N = 75, 90.3 (89.7)	N = 111, 90.5 (78.7)	0.4226*7	N = 1037, 181.1 (129.4)	N = 354, 190.5 (118.6)	N = 683, 176.3 (134.3)	p = 0.03*7
anxiolytic and hypnotics	66.5	66.4	66.6	0.9765*6	74.4	72.1	75.7	p = 0.1887*6
mean number of anxiolytic and hypnotics	N = 1448, 1.7 (0.8)	N = 655, 1.7 (0.8)	N = 793, 1.6 (0.8)	0.3007*7	N = 921, 1.8 (0.8)	N = 312, 1.8 (0.8)	N = 609, 1.8 (0.9)	p = 0.9523*7
mean dose of anxiolytic and hypnotics (mg/day)*4	N = 1179, 14.5 (13.4)	N = 546, 15.3 (14.1)	N = 633, 13.8 (12.8)	0.0202*7	N = 633, 11.4 (10.8)	N = 209, 11.7 (10.3)	N = 424, 11.3 (11.1)	p = 0.6456*7
mood stabilizer and antiepileptics	26.9	28.2	25.8	0.2231*6	18	18.9	17.5	p = 0.5869*6
mean number of mood stabilizer and antiepileptics	N = 585, 1.1 (0.4)	N = 278, 1.1 (0.4)	N = 307, 1.1 (0.3)	0.401*7	N = 223, 1.1 (0.3)	N = 82, 1.1 (0.4)	N = 141, 1.1 (0.3)	p = 0.3497*7
other psychotropics	1.1	1.2	1.1	0.943*6	1.7	1.6	1.7	p = 1.0*6
mean number of other psychotropics	N = 25, 1 (0.2)	N = 12, 1 (0)	N = 13, 1.1 (0.3)	1*7	N = 21, 1.1 (0.3)	N = 7, 1 (0)	N = 14, 1.1 (0.3)	p = 0.5333*7

Mean (S.D.) except for (%)

Mean number and mean dose were the results in the prescribed subjects.
*1: chlorpromazine equivalent, *2: benztropine equivalent, *3: imipramine equivalent, *4:diazepam/nitrazepam equivalent, *5: t test, *6: chi-square test, *7: Wilcoxon test, §; $p < 0.001$.

subjects were prescribed anti-parkinson drugs, 9.2 % antidepressants, 66.5 % anxiolytics and hypnotics, 26.9 % mood stabilizers and antiepileptics, and 1.1 % other drugs. Compared to the male subjects, the female subjects received a lower dose of antipsychotics (637.2 ± 428.6 (mean ± S.D.) mg/day vs. 739.6 ± 470.5 mg/day). This difference holds in the analysis of atypical antipsychotics only. The percentage of prescribed subjects, daily dose, and number of drugs prescribed to the subjects in other categories were not different between sexes.

Regarding the patients with MDD, 84.2 % of the subjects were prescribed antidepressants, and the mean number of antidepressants was

Table 2
Demographic background and prescription of psychotropics (analysis for number of antipsychotics or antidepressants).

	Schizophrenia(N = 2177)				Major Depressive Disorder (N = 1238)			
	no antipsychotic	mono antipsychotic	poly antipsychotics	p*5	no antidepressant	mono antidepressant	poly antidepressant	p*5
N (male)	74 (male = 28)	1169 (male = 502)	934 (male = 456)	p < 0.0001*6,§	195 (male = 76)	729 (male = 252)	314 (male = 105)	p < 0.0001*6,§
age	53 (17.1)	45.5 (15.7)	46.1 (14.7)	p = 0.4107*7	51.7 (19.9)	59 (17.4)	59.5 (16.9)	p = 0.668*7
antipsychotics (%)(≥3 drugs for SZ, ≥1 drug for MDD)	–	–	24.1	p < 0.0001*6,§	60	48.7	58.6	p = 0.0041*6
mean number of antipsychotics	–	N = 1169, 1 (0)	N = 934, 2.3 (0.6)	P<0.0001*8,§	N = 117, 1.1 (0.4)	N = 355, 1.1 (0.3)	N = 184, 1.1 (0.3)	p = 0.647*8
mean dose of antipsychotics (mg/day)*1	–	N = 1166, 469.2 (262.6)	N = 934, 951.8 (492.1)	P<0.0001*8,§	N = 117, 249.2 (282.8)	N = 349, 166.5 (159.3)	N = 160, 158.6 (129.5)	p = 0.729*8
typical antipsychotics (%)	–	6.8	53.3	p < 0.0001*6,§	9.7	6.2	16.6	p < 0.0001*6,§
mean number of typical antipsychotics	–	N = 80, 1 (0)	N = 498, 1.3 (0.5)	p < 0.0001*8,§	N = 19, 1 (0)	N = 45, 1.1 (0.2)	N = 52, 1 (0.2)	p = 0.5393*8
mean dose of typical antipsychotics (mg/day) *1	–	N = 81, 292.7 (336.5)	N = 493, 260.3 (304.7)	p = 0.1314*8	N = 19, 82.6 (102.1)	N = 39, 42.5 (44)	N = 21, 40.7 (39.4)	p = 0.0001*8,§
atypical antipsychotics (%)	–	93.2	93.5	p = 0.8439*6	54.4	43.9	45.5	p = 0.6725*6
mean number of atypical antipsychotics	–	N = 1089, 1 (0)	N = 873, 1.7 (0.6)	P<0.0001*8	N = 106, 1.1 (0.3)	N = 320, 1.1 (0.3)	N = 143, 1.1 (0.3)	p = 0.7588*8
mean dose of atypical antipsychotics (mg/day) *1	–	N = 1089, 480.6 (252.4)	N = 873, 871.3 (456.5)	P<0.0001*8	N = 106, 260.2 (275.7)	N = 320, 176.4 (160.9)	N = 143, 171.4 (129.9)	p = 0.4995*8
anti-Parkinson drugs (%)	6.8	21	43.3	p < 0.0001*6,§	8.2	4.1	4.8	p = 0.7517*6
mean number of anti-Parkinson drugs	N = 5, 1 (0)	N = 246, 1.1 (0.2)	N = 404, 1.1 (0.3)	p = 0.1091*8	N = 16, 1.1 (0.3)	N = 30, 1.1 (0.3)	N = 15, 1 (0)	p = 0.2203*8
mean dose of anti-Parkinson drugs (mg/day)*2	N = 5, 2.4 (0.5)	N = 242, 2.4 (1.4)	N = 394, 2.8 (1.6)	p = 0.0006*8,§	N = 12, 2.4 (1.3)	N = 24, 1.7 (0.7)	N = 12, 1.6 (1.2)	p = 0.2822*8
antidepressant (%)(≥1 drug for SZ, ≥3 drug for MDD)	8.1	7.7	11.1	p = 0.0086*6	–	–	12.7	p < 0.0001*6,§
mean number of antidepressant	N = 6, 1.2 (0.4)	N = 90, 1.1 (0.3)	N = 104, 1.1 (0.3)	p = 0.7404*8	–	N = 729, 1 (0)	N = 314, 2.1 (0.4)	P<0.0001*8,§
mean dose of antidepressant (mg/day)*3	N = 6, 152.1 (128.4)	N = 88, 87.5 (86.1)	N = 92, 89.2 (74.9)	p = 0.7226*8	–	N = 723, 145.3 (110.6)	N = 314, 263.7 (131.6)	P<0.0001*8,§
anxiolytic and hypnotics	39.2	59.9	77	p < 0.0001*6,§	63.1	73.1	84.4	P = 0.0001*6,§
mean number of anxiolytic and hypnotics	N = 29, 1.4 (0.6)	N = 700, 1.6 (0.7)	N = 719, 1.8 (0.9)	P<0.0001*8,§	N = 123, 1.7 (0.8)	N = 533, 1.7 (0.8)	N = 265, 1.9 (0.9)	p = 0.0094*8
mean dose of anxiolytic and hypnotics (mg/day)*4	N = 23, 12.4 (11.1)	N = 569, 12.5 (11.1)	N = 587, 16.4 (15.1)	P<0.0001*8,§	N = 80, 11.8 (9.3)	N = 368, 10.9 (10.7)	N = 185, 12.5 (11.6)	p = 0.0298*8
mood stabilizer and antiepileptics	13.5	21.4	34.8	p < 0.0001*6,§	36.9	14.7	14	p = 0.854*6
mean number of mood stabilizer and antiepileptics	N = 10, 1.1 (0.3)	N = 250, 1.1 (0.3)	N = 325, 1.2 (0.4)	p = 0.0391*8	N = 72, 1.2 (0.4)	N = 107, 1.1 (0.3)	N = 44, 1.1 (0.4)	p = 0.5791
other psychotropics	1.4	0.9	1.4	p = 0.4469*6	1	1.8	1.9	p = 1.0*6
mean number of other psychotropics	N = 1, 1 (NA)	N = 11, 1.1 (0.3)	N = 13, 1 (0)	p = 0.4583*8	N = 2, 1 (0)	N = 13, 1.2 (0.4)	N = 6, 1 (0)	p = 0.5439
Mean (S.D.) except for (%)								

Mean number and mean dose were the results in the prescribed subjects.
*1: chlorpromazine equivalent, *2: benztropine equivalent, *3: imipramine equivalent, *4: diazepam/nitrazepam equivalent, *5: comparison between mono antipsychotics vs poly antipsychotics for schizophrenia and mono antidepressant vs poly antidepressants for MDD, *6: chi-square test, *7: t test, *8: Wilcoxon test, §; p < 0.001.

1.3 ± 0.6 (mean ± S.D.), with the imipramine equivalent daily dose of 181.1 ± 129.4 mg/day. No differences were found in the prescription rates of antidepressants, antipsychotics, anxiolytics or hypnotics, and mood stabilizers or antiepileptics between sexes. Equivalent daily doses of antidepressants, antipsychotics, anxiolytics or hypnotics did not differ between sexes (Table 1).

3.2. Comparison between age groups

For the subjects with schizophrenia, those aged between 60 and 79 were prescribed a lower dose of antipsychotics (260.5 ± 201.9) than the subjects aged between 20 and 39 or the subjects aged between 40 and 59. Regarding anxiolytics and hypnotics, the subjects aged between 60 and 79 were prescribed lower doses (12.1 ± 11.1) than the subjects aged between 30 and 59. For the patients with MDD, the dose of antidepressants did not differ between any of the 5 age groups (Fig. 2). There were significant differences between the percentage of subjects with schizophrenia who were prescribed antipsychotics and the percentage of subjects with MDDs who were prescribed antidepressants in the age groups under 20, between 20 and 39 and between 40 and 59 (Fig. 2).

3.3. Comparison between monotherapy versus polytherapy of antipsychotics and antidepressants

In all, 1169 subjects with schizophrenia received antipsychotic monotherapy (53.7 %), 934 subjects (42.9 %) received poly (two or more) antipsychotics, and 74 subjects (3.4 %) did not receive any antipsychotics at all (Table 2). The frequency of concomitant drugs such as anti-Parkinson drugs (21 % vs. 43.3 %), anxiolytics and hypnotics (59.9 % vs. 77 %) and mood stabilizers (21.4 % vs. 34.8 %) in the subjects with schizophrenia prescribed antipsychotic polypharmacy was significantly higher than that in the subjects prescribed antipsychotic monotherapy. The subjects with schizophrenia on antipsychotic polypharmacy who were prescribed hypnotics and anxiolytics received a higher number (1.6 ± 0.7 vs. 1.8 ± 0.9) and higher amount (12.5 ± 11.1 vs. 16.4 ± 15.1) than those with antipsychotic monotherapy.

On the other hand, 729 subjects (58.9 %) with MDDs received antidepressant monotherapy, 314 subjects (25.4 %) with MDDs received two or more antidepressants, and 195 subjects (15.7 %) with MDDs did not receive any antidepressants (Table 2). The mean number and equivalent daily dose of antidepressants for MDD significantly differed (Table 2, Fig. 1). The frequency of concomitant drugs of typical antipsychotics (6.2 % vs. 16.6 %) and anxiolytics and hypnotics (73.1 % vs. 84.4 %) in the subjects with MDDs prescribed antipsychotic polypharmacy was significantly higher than that in the subjects with MDDs prescribed antipsychotic monotherapy.

3.4. Most often prescribed psychotropics

Table 3 shows the five most often prescribed psychotropics in each category in the patients with schizophrenia and MDD. For the patients with schizophrenia, olanzapine, risperidone, aripiprazole, quetiapine, and blonanserin were the five most prescribed antipsychotics. For the patients with MDD, mirtazapine, duloxetine, escitalopram, trazodone and sertraline were the five most prescribed antidepressants. Regarding anxiolytics and hypnotics, flunitrazepam was the most often prescribed drug in both schizophrenia and MDD. Information about other antipsychotics is shown in Supplementary Table 2 for schizophrenia and Supplementary Table 3 for MDD.

Among the antipsychotics used in more than 10 cases in schizophrenia, levomepromazine (96.8 %), followed by zotepine (92.2 %), were the most frequently used drugs in combination with other antipsychotics, while clozapine (11.7 %) was the least frequently used (Supplementary Table 4). The most frequent concomitant use of anti-Parkinson drugs was haloperidol (70.7 %), followed by zotepine (57.8 %). Asenapine (14.3 %) was the antipsychotic most frequently used with antidepressants, followed by quetiapine (12.4 %). Furthermore, zotepine (84.4 %), followed by chlorpromazine (81.1 %), was the most frequently used antipsychotic in combination with anxiolytics and hypnotics. Zotepine (44.4 %), followed by chlorpromazine (42.5 %), was also frequently used with mood stabilizers. Among the antidepressants used in more than 10 MDD patients, mianserin (77.8 %) was the most frequently used antidepressant in combination with other antidepressants, followed by trazodone (72.7 %), while venlafaxine (32.9 %) was the least frequently used (Supplementary Table 5). The antidepressant most frequently used in combination with antipsychotics was amoxapine (74.4 %), followed by fluvoxamine (70.8 %). The most frequent concomitant use of anti-Parkinson drugs was amoxapine (12.8 %), followed by milnacipran (9.1 %). Furthermore, the medication most frequently concomitantly used with anxiolytics and hypnotics was milnacipran (86.4 %), followed by duloxetine (84.2 %). Fluvoxamine (33.3 %), followed by amoxapine (30.8 %), was also frequently used with mood stabilizers.

3.5. Comparison between types of hospitals (university hospitals/other centers)

The rate of prescription of antipsychotic drugs for schizophrenia was low in private general hospitals (66.7 %), while the rate of prescription of anti-Parkinson drugs was high (60 %) (Supplementary Table 6). There

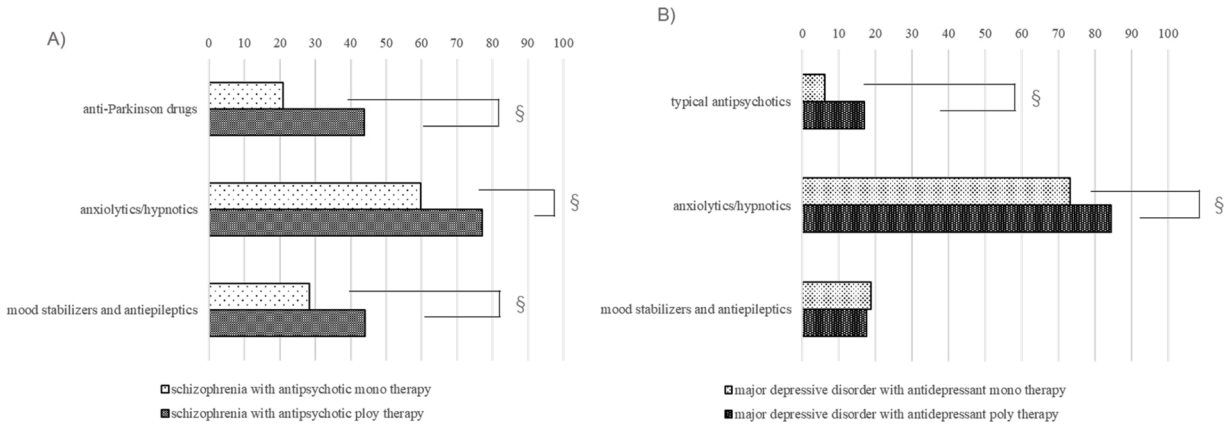

Fig. 1. Comparisons of concurrent use of psychotropics between mono and poly therapy of antipsychotics in patients with schizophrenia and that of antidepressant in patient with major depressive disorder.
Comparisons of concurrent use of psychotropics between mono and poly therapy of antipsychotics in patients with schizophrenia (A), and those of antidepressant in patient with major depressive disorder(B). §; Wilcoxon test, $p < 0.0001$.

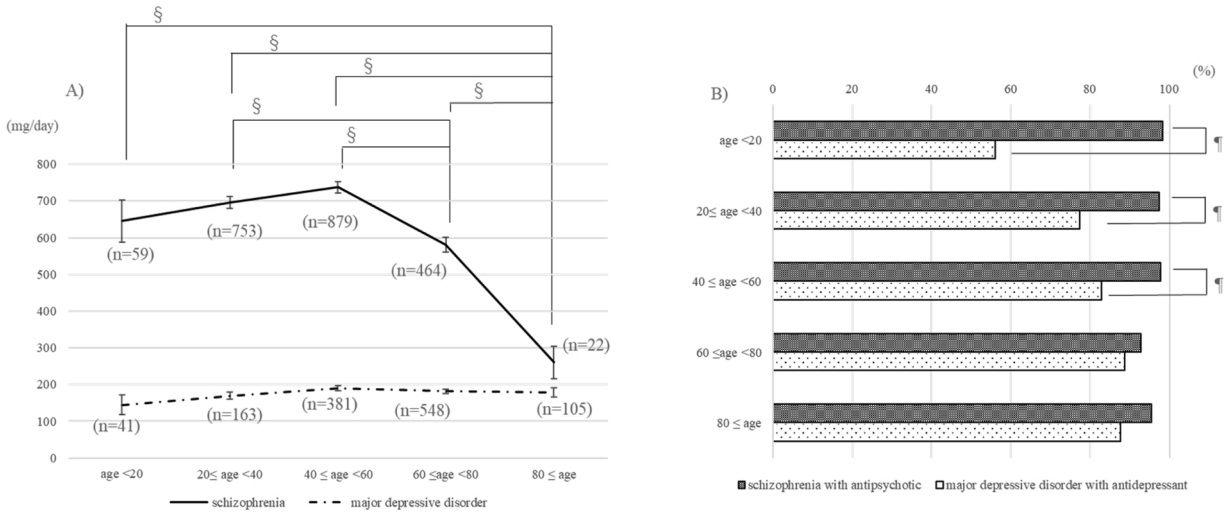

Fig. 2. Age and prescription of antipsychotics in patients with schizophrenia and that of antidepressants in major depressive disorder.
A) Daily dose of chlorpromazine equivalent daily dose of antipsychotics (schizophrenia) and imipramine equivalent daily dose of antidepressants (major depressive disorder) by age groups. B) Comparison of percentage of schizophrenia patients prescribed antipsychotics and major depressive disorder who prescribed antidepressants in each age group. Error bar: standard error, §; Dunn-Bonferroni test, $p < 0.0001$, ¶; chi-square test, $p < 0.016$.

Table 3
The five most often prescribed psychotropics in each category.

Schizophrenia (N = 2177)				Major Depressive Disorder (N = 1238)			
drug name	N	Daily dose*1	Daily dose (eq)*2	drug name	N	Daily dose*1	Daily dose (eq)*2
antipsychotic drugs				antipsychotic drugs			
olanzapine	531	14.3(6.3)	570.9(252)	quetiapine	203	108.7(117.1)	165.3(178)
risperidone	486	4.9(3)	488.2(304.8)	aripiprazole	164	5.9(4.9)	147.2(122.6)
aripiprazole	395	18.1(8.6)	451.4(215.4)	olanzapine	147	6(4.3)	239.7(173)
quetiapine	315	295.4(231.2)	449(351.5)	risperidone	65	1.4(1)	136.9(97.7)
blonanserin	258	16.6(7.5)	414.5(186.3)	levomepromazine	47	33.3(33.2)	33.3(33.2)
anti-Parkinson drugs				anti-Parkinson drugs			
biperiden	514	2.6(1.4)	2.6(1.4)	biperiden	29	2(1.2)	2(1.2)
trihexyphenidyl	86	4.6(2)	2.3(1)	promethazine	11	34.3(24)	1.4(1)
promethazine	70	40.4(28.6)	1.6(1.1)	trihexyphenidyl	7	3.6(1.3)	1.8(0.6)
amantadine	6	116.7(47.1)	2.3(0.9)	pramipexole	6	0.7(0.6)	–
pramipexole	6	0.5(0.3)	–	rotigotine	3	7.2(4.9)	–
antidepressants				antidepressants			
trazodone	70	60.7(37.2)	30.4(18.6)	mirtazapine	393	30.8(12.9)	153.9(64.3)
mirtazapine	35	27.9(11.3)	139.3(56.4)	duloxetine	196	45.4(14.9)	226.8(74.5)
escitalopram	16	11.9(5)	89.1(37.2)	escitalopram	175	17.5(15.1)	131.6(113.5)
duloxetine	15	37.3(14.4)	186.7(71.8)	trazodone	132	56(39.6)	28(19.8)
sertraline	15	46.7(25.6)	70(38.4)	sertraline	103	79.5(27.6)	119.2(41.5)
anxiolytics/hypnotics				anxiolytics/hypnotics			
flunitrazepam	485	1.8(0.8)	8.9(3.8)	flunitrazepam	222	1.7(0.7)	8.6(3.4)
brotizolam	250	0.3(0.1)	5.7(1.8)	suvorexant	216	17.2(2.6)	–
clonazepam	240	1.3(0.8)	25.6(16.9)	brotizolam	186	0.3(0.4)	6(7.1)
nitrazepam	230	8.3(3.2)	8.3(3.2)	lorazepam	125	1.4(1.8)	5.9(7.4)
suvorexant	207	18.4(2.4)	–	zolpidem	113	7.7(2.7)	3.9(1.3)
mood stabilizer/ antiepileptics				mood stabilizer/ antiepileptics			
sodium valproate	399	657.9(283.4)	–	lithium carbonate	103	416.5(197.6)	–
lithium carbonate	133	582.7(249.4)	–	sodium valproate	64	488.4(264.2)	–
carbamazepine	76	484.9(254.4)	–	lamotrigine	54	163(100.3)	–
lamotrigine	23	131.8(84.4)	–	carbamazepine	14	392.9(183.1)	–
topiramate	10	170(105.4)	–	gabapentin	3	600(163.3)	–
other psychotropics				other psychotropics			
atomoxetine hydrochloride	9	82.2(38.2)	–	memantine	7	17.1(4.5)	–
memantine	6	17.5(3.8)	–	donepezil	6	6(2.3)	–
donepezil	5	5(0)	–	atomoxetine hydrochloride	2	70(10)	–
methylphenidate hydrochloride	2	45(27)	–	galantamine	2	12(4)	–
rivastigmine skin patch	2	18(0)	–	acamprosate calcium	2	1998(0)	–

*1: Mean(S.D.) (mg/day), *2: Mean(S.D.) (mg/day): chlorpromazine equivalent for antipsychotics, benztropine equivalent for anti-Parkinson drugs, imipramine equivalent for antidepressant, diazepam/nitrazepam equivalent for anxiolytics and hypnotics, *3: Wilcoxon test (Bonferroni correction for multiple comparisons).

was no difference in the rate of antidepressant prescriptions between institutions. The prescription rate of anxiolytics and hypnotics was lower in private psychiatric hospitals (53 %). The prescription rate of emotion stabilizers was higher in private general hospitals (53.3 %). The prescription rate of antidepressants for depression was highest in public general hospitals (90.1 %) and lowest in public psychiatric hospitals

(71.4 %) (Supplementary Table 7). This was also the case for anxiolytics and hypnotics. The prescription rate of antipsychotics was the highest in private general hospitals (67.9 %) and the lowest in efficient general hospitals (59.4 %), but the difference itself was small.

4. Discussion

In the current study, we summarized the prescription data at discharge in 2177 patients with schizophrenia and 1238 patients with MDD from 83 institutions in Japan from 2016 to 2018. Regarding schizophrenia, our data showed that the female subjects with schizophrenia received lower doses of antipsychotics and hypnotics and anxiolytics than the male subjects with schizophrenia, but this difference was not observed in the female and male subjects with MDD. The patients with schizophrenia prescribed antipsychotic polypharmacy received more anti-Parkinson drugs and higher doses of hypnotics and anxiolytics than those prescribed antipsychotic monopharmacy. With regard to MDD, no differences were found in antidepressant doses between ages. In addition, the patients with schizophrenia aged between 60 and 79 were prescribed lower doses of antipsychotics and hypnotics and anxiolytics than those aged between 40 and 59, while no difference was found in doses of antidepressants in the patients with MDD among the 5 age groups. There were significant differences between the percentage of subjects with schizophrenia who were prescribed antipsychotics and the percentage of subjects with MDDs who were prescribed antidepressants in the age groups under 20, between 20 and 39 and between 40 and 59 years.

In our data, the chlorpromazine equivalent daily dose of antipsychotics was 680.7 ± 445.1 mg/day, and the percentage of patients with schizophrenia who received antipsychotic polypharmacy was 43.1 %. In the outpatient data for 2012, the daily dose of antipsychotics was 228.7 mg/day (risperidone equivalent 2.287 mg/day), and 15.3 % of the subjects were prescribed antipsychotic polypharmacy (Hata et al., 2020). The discrepancy may be explained by the fact that inpatients are more severely ill than outpatients. In a previous review, antipsychotic combination treatment was applied to 10%–20% of schizophrenic outpatients, whereas 50 % of schizophrenic inpatients received more than 2 antipsychotics (Stahl and Grady, 2004). In the 2016 inpatient data for Japan, 55 % of the subjects were prescribed antipsychotic polypharmacy (Yang et al., 2018), which was in line with our data. This is the second highest percentage among 15 Asian countries in the REAP study, and 4 countries accounted for less than 30 %. Antipsychotic polypharmacy prescribed at discharge accounted for 21.2 % of treatments in Turkey in 2017 (Civan Kahve et al., 2020). Considering these data, 30 % or less for antipsychotic polypharmacy in prescriptions at discharge seems to be reasonable as a future goal. Although whether antipsychotic polypharmacy is more effective than monotherapy is controversial (Pae, 2020), avoidance of unnecessary polypharmacy is essential to prevent and minimize potentially adverse drug reactions (Yasui-Furukori and Shimoda, 2020).

The concomitant use of anti-Parkinson drugs with anxiolytic and hypnotic symptoms was more often associated with antipsychotic polypharmacy than monotherapy in patients with schizophrenia. Regarding anxiolytics and hypnotics, 66.6 % of the patients were prescribed this type of drug, which increased to 77.1 % in the subjects prescribed antipsychotic polypharmacy, and most of these drugs were benzodiazepines. These percentages were in line with the 61 % concomitant use of hypnotics in Japan in the REAP study (Yang et al., 2018). However, in the REAP study, the average percentage of concomitant use of hypnotics in 15 countries was 9.3 %, and the percentage for Japan was extraordinarily high. The concomitant use of benzodiazepine was 32 % in the AMSP study (Toto et al., 2019). A recent review article and meta-analysis did not verify the efficacy of concomitant use of benzodiazepines compared to antipsychotics (Dold et al., 2013; Sim et al., 2015). Moreover, the concomitant use of benzodiazepine with antipsychotics has been associated with a significant increase in mortality (Tiihonen et al., 2012). The decrease in concomitant use of benzodiazepine, especially among subjects with antipsychotic polypharmacy, is an urgent problem in Japan. Although the polypharmacy of antidepressants in MDD was lower than that of antipsychotics in schizophrenia, the concomitant use of typical antipsychotics and anxiolytics and hypnotics was more often associated with antidepressant polypharmacy than monotherapy in patients with MDD, which is the first report of this finding.

Female subjects with schizophrenia received lower doses of antipsychotics than male subjects with schizophrenia, but this difference was not observed in female and male subjects with MDD. A previous study in Japan showed that the ratio of subjects who were prescribed antipsychotics in the dose range “lower than the recommended dose range” was not different between males and females (Tsutsumi et al., 2011). However, sex differences in blood flow, the size of the liver (especially in the case of agents metabolized by CYP3A4), and hormones (estrogen is an inhibitor of cytochrome P (CYP) 1A2) could impact drug clearance (Bies et al., 2003). Therefore, it may be rational to set the dose of the antipsychotics lower in females.

The subjects with schizophrenia aged between 60 and 79 received lower doses of antipsychotics than those aged between 20 and 39 or between 40 and 59, but these differences were not observed in the subjects with MDD. Our results were in line with previous studies showing an inverted U-shaped relationship between age and the dose of antipsychotics (Sproule et al., 2010; Uchida et al., 2008). In general, elderly patients can obtain therapeutic effects and experience side effects more often from lower doses of antipsychotics than younger subjects (Uchida et al., 2009). Patients with schizophrenia aged >65 years are characterized by a high burden of medical illnesses (Chen et al., 2020). Age-related increases in brain access and decreases in endogenous dopamine levels and the dopamine receptor density were thought to be related to this (Uchida et al., 2009). On the other hand, such a tendency was not found between age and the dose of antidepressants in this study. A recent meta-analysis showed that there was no relationship between drug dosages and response rates (Gutsmiedl et al., 2020).

The 5 antipsychotics most frequently prescribed for schizophrenia were olanzapine, risperidone, aripiprazole, quetiapine, and blonanserin, all of which are atypical antipsychotics, and this finding is in line with Japanese expert consensus regarding aripiprazole, risperidone, olanzapine, and quetiapine as first-line treatments (Sakurai et al., 2021). On the other hand, the 5 most frequently prescribed antidepressants were mirtazapine, duloxetine, escitalopram, trazodone, and sertraline. Other than trazodone, these drugs are newly generated antidepressants, and this finding is partially in line with Japanese expert consensus regarding mirtazapine, duloxetine, escitalopram, and sertraline but not trazodone as first-line treatments (Sakurai et al., 2020). Recent guidelines recommend seven representative antidepressants: agomelatine, amitriptyline, bupropion, escitalopram, mirtazapine, venlafaxine, and vortioxetine (Malhi et al., 2020). In the US, sertraline, fluoxetine, citalopram, bupropion, and escitalopram are among the most frequently prescribed antidepressants (Luo et al., 2020). Surprisingly, the prescription rate of mirtazapine was only 1.1 % in 2015 (Luo et al., 2020), which was quite different from our study. In addition, the equivalent daily doses of the 5 antipsychotics in patients with schizophrenia were similar, whereas the equivalent daily dose of trazodone was low compared with those of the other 4 antidepressants in patients with MDD. In addition, the dose of trazodone (56 mg/day) was much lower than that in the US (140 mg/day) (Luo et al., 2020). This may make trazodone’s targeted symptoms different from those of other antidepressants in Japan (Sakurai et al., 2020).

The strengths of this study are that the diagnoses were confirmed by the treating psychiatrists, all data were based on prescriptions at discharge and were unlikely to be under drug adjustment, and a large multicenter dataset consisting of 2177 patients with schizophrenia and 1238 patients with MDD from 83 institutions gathered from all over Japan was generated.

5. Limitation

There are several limitations in this study. First, we did not assess the symptom severity of schizophrenia or MDD using rating scales such as the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), the Hamilton MDD Scale (HAMD) or the Montgomery-Åsberg MDD Rating Scale (MADRS). Second, although we set a standardized data collection method, the data were basically collected from medical records that the collaborating investigators obtained in routine clinical settings, which might impact the results. Third, although our data were gathered from all over Japan, all participating sites were institutions that voluntarily cooperated with the study, and there is a possibility of selection bias. There is also bias in the types of hospitals, with almost half being university hospitals, which may make it difficult to generalize the results even though significant differences were found among types of hospitals.

6. Conclusions

In the current study, we assessed prescriptions made at discharge before psychiatrists received special instructions regarding guidelines. Our results showed a high dose of antipsychotics, a high percentage of antipsychotic polypharmacy and concurrent use of hypnotics and anxiolytics prescribed for patients with schizophrenia. Although these findings were in line with previous data (Hata et al., 2020; Yang et al., 2018), they do not meet the recommendations of the guidelines, and there may be room for improvement in terms of international comparison. We are currently gathering follow-up data from the same psychiatrists and will assess the changes in prescription patterns after these psychiatrists receive special instructions regarding the guidelines.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ajp.2021.102744.

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