Prescribing trends for the same patients with schizophrenia over 20 years

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May 25, 2022

Abstract

BACKGROUND: Recent pharmacoepidemiology data show an increase in the proportion of patients receiving second-generation antipsychotic (SGA) monotherapy, but no studies have analyzed the same patients over a long period of time. Therefore, in this study, we decided to evaluate retrospectively schizophrenia patients with available data for 20 years to see whether the drug treatments in the same patients have changed in the past 20 years. METHODS: The study began in April 2021 and was conducted in 15 psychiatric hospitals in Japan. Schizophrenia patients treated in the same hospital for 20 years were retrospectively examined for all prescriptions in 2016, 2011, 2006, and 2001 (i.e., every 5 years). RESULTS: The mean age of the 716 patients surveyed in 2021 was 61.7 years, with 49.0% being female. The rate of antipsychotic monotherapy use showed a slight increasing trend over the past 20 years; the rate of SGA use showed a marked increasing trend from 28.9% to 70.3% over the past 20 years, while the rate of SGA monotherapy use showed a gradual increasing trend over the past 20 years. The rates of concomitant use of anticholinergics, antidepressants, anxiolytics/sleep medications, and mood stabilizers showed decreasing, flat, decreasing, and flat trends over the past 20 years, respectively. CONCLUSION: The results of this study showed a slow but steady substitution of SGAs for first-generation antipsychotics (FGAs) over time, even in the same patients.

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Running title: Antipsychotics and 20 years trends

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Word count: 3544 Table count: 3 Figure count: 3

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METHODS : The study began in April 2021 and was conducted in 15 psychiatric hospitals in Japan. Schizophrenia patients treated in the same hospital for 20 years were retrospectively examined for all prescriptions in 2016, 2011, 2006, and 2001 (i.e., every 5 years).

RESULTS : The mean age of the 716 patients surveyed in 2021 was 61.7 years, with 49.0% being female. The rate of antipsychotic monotherapy use showed a slight increasing trend over the past 20 years; the rate of SGA use showed a marked increasing trend from 28.9% to 70.3% over the past 20 years, while the rate of SGA monotherapy use showed a gradual increasing trend over the past 20 years. The rates of concomitant use of anticholinergics, antidepressants, anxiolytics/sleep medications, and mood stabilizers showed decreasing, flat, decreasing, and flat trends over the past 20 years, respectively.

CONCLUSION : The results of this study showed a slow but steady substitution of SGAs for first-generation antipsychotics (FGAs) over time, even in the same patients.

Keywords

pharmacoepidemiology, prescription, antipsychotics, trends, schizophrenia

Introduction

Schizophrenia is a chronic psychiatric disorder that is associated with positive and negative symptoms as well as cognitive dysfunction and a significant decline in psychosocial functioning.[1] The combination of

pharmacotherapy with antipsychotics and psychotherapy, such as psychosocial rehabilitation, is considered to be a treatment that can improve not only the psychiatric symptoms of patients with schizophrenia but also their cognitive and social functioning.[1,2] Schizophrenia often requires long-term treatment with antipsychotic drugs. Historically, treatment with a wide variety of antipsychotics has had an uncertain impact on patient-centered long-term outcomes such as stable employment, maintenance of good interpersonal relationships, and maintenance of independent living, and there are serious concerns about side effects (such as tardive dyskinesia, weight gain, diabetes, and dyslipidemia) with some treatments.[3] Older first-generation antipsychotics (FGAs), such as haloperidol, have proven effective, but side effects such as extrapyramidal symptoms (EPSs) and, in some cases, tardive dyskinesia often limit long-term adherence. Since the 1990s, second-generation antipsychotics (SGAs), which are equally effective and have fewer side effects than FGAs, have become mainstream.[4-6]Second-generation antipsychotic (SGA) are expected to be equally or more effective than FGAs, especially for negative symptoms, and are expected to reduce EPSs and the risk of tardive dyskinesia. However, SGAs also have potentially serious side effects (e.g., cardiovascular and endocrine side effects), and the overall risk-benefit profile is less clear than expected.

Many guidelines state that pharmacotherapy is important in the treatment of schizophrenia, and from various perspectives in these guidelines, monotherapy with an SGA is considered ideal.[7-11]Previous studies have shown that SGAs are more commonly used than FGAs; an international study examined international trends in antipsychotic use in 16 countries in 2005 and found an increase in SGA use in all study populations in 2014, but the pattern of antipsychotic use varied widely across countries.[12] From the database of prescription data of the international drug safety program, the prescription data of inpatients with schizophrenia from 2000 to 2015 showed that the use of SGAs significantly increased from 62.8% to 88.9%, and the prescription rate of FGAs decreased from 46.6% to 24.7%.[13] In Japan, 82.3% of adult patients with schizophrenia were treated with monotherapy, and 17.8% were treated with multidrug therapy, with risperidone being the most commonly prescribed monotherapy (20.8%) between 2006 and 2012.[14] Between 2006 and 2012, a year-to-year increase in the proportion of SGA monotherapy was seen in adult and elderly patients, and a decrease in antipsychotic doses was seen among adults.[14] Up to 81% of a study cohort of Japanese patients with chronic schizophrenia were taking daily antipsychotic medication at doses exceeding an average of 1000 mg chlorpromazine equivalents (CPeq) per day.[15] In a study covering six East Asian countries and regions, Sim et al. found that 17.9% of their sample was prescribed high doses of antipsychotics.[16]

Such previous studies looking at trends in prescribing have been limited to comparisons of cross-sectional data from period to period. Some of these data may or may not include the same patients. However, there are currently no studies that follow prescribing trends over a long period of time for the same patients. In actual clinical practice, few patients start treatment with FGAs.[12] While a recent report from a combination of FGA and SGA indicates that monotherapy improves psychiatric symptoms and does not increase relapse, regardless of FGA or SGA,[17] easy monotherapy to SGA is believed to be associated with the risk of relapse. Thus, once FGA treatment is switched to SGA treatment in chronically ill patients who had been treated for a long time with FGA, the mental state of the patient often becomes unstable, and for many such patients, FGAs are continued. We, therefore, hypothesized that patients whose symptoms stabilized on FGAs would be less likely to switch to SGAs and that the proportion of patients using SGAs would be lower than those in previous studies. Therefore, in this study, we examined whether the medication regimens of schizophrenia patients with available data for the past 20 years changed over this time period.

Methods

In this pharmacoepidemiological study, we investigated real-life prescribing trends related to psychotropic drugs in schizophrenia patients at Dokkyo Medical University Hospital and its affiliated hospitals. The study was initiated in April 2021 and was conducted in 15 psychiatric hospitals. To avoid sampling bias, we enrolled up to 70 consecutive patients with schizophrenia attending each hospital from April 1, 2021, whose prescriptions could be traced over the past 20 years; for institutions that did not reach 70 patients, all patients were enrolled. We retrospectively examined all prescriptions as of April 1, 2016, 2011, 2006, and 2001, every 5 years starting in 2021, for this population. Consensus meetings were held at each site prior to the study

to discuss issues related to data collection and the uniformity of data entry. The participating patients met the diagnostic criteria for schizophrenia in the International Classification of Diseases, Tenth Edition (ICD-10)[18] or the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[19]Patients with clinically significant medical illnesses or active psychotic symptoms related to comorbid substance use disorders were excluded.

The data collected included basic sociodemographic information and information on all prescribed medications. Daily doses of antipsychotic drugs were calculated using the equations in the Inada & Inagaki article as average daily CPeq, imipramine equivalents, and diazepam equivalents.[20] This study was approved by the Ethics Committee of Dokkyo Medical University Hospital (Ref. R-54-3J).

Statistical Package for Social Sciences (SPSS) Version 28 (SPSS Inc., Chicago, IL, USA) was used for analysis. The Cochran Q test and repeated-measures analysis of variance (ANOVA) and were used to determine the differences among the five groups. Although statistical significance required a two-sided $P<0.05$, these were adjusted by Bonferroni's correction to avoid multiplicity, and $P < 2.5 \times 10^{-3}$ (0.05/20) was defined as significant. Cochran–Armitage trend test and the Pearson correlation test were used to determine the trends. There statistical significances required a two-sided $P<0.05$

Results

The mean (SD) age of the 716 patients in the study in 2021 was 61.7 (11.5) years; 51.0% (n=365) of patients were males and 49.0% (n=351) were females. The proportion of patients with a history of hospitalization was 51.1% (n=366).

Trend of antipsychotic monotherapy

The rate of antipsychotic monotherapy in 2001, 2006, 2011, 2016 and 2021 were 32.0%, 33.7%, 32.8%, 37.6% and 41.5%, respectively, and the rate of dual-agent antipsychotic use were 36.7%, 37.4%, 39.4%, 41.9% and 41.9%, respectively (Table 1). The rate of patients taking three or more drugs were 18.7%, 18.5%, 18.0%, 14.0% and 9.4%, respectively (Table 1).

The average number of antipsychotic medications taken trended downward from 2.0 to 1.7 ($r = -0.938$, $p = 0.018$) (Table 2). The percentage of patients receiving complete antipsychotic monotherapy without psychotropic medications other than antipsychotics in 2001, 2006, 2011, 2016 and 2021 were only 2.5%, 4.5%, 5.9%, 7.7% and 8.8%, but and increased significantly ($\chi2 = 32.3$, $df = 1$, $p = 1.3\text{x}10^{-8}$) (Fig 1). On the other hand, the rate of SGA use in 2001, 2006, 2011, 2016 and 2021 were 28.9%, 49.2%, 61.4%, 65.4% and 70.5%, respectively, and when analyzing the prescription rates of these drugs over the past 20 years, the trend over the past 20 years was an increasing trend ($\chi2 = 286.2$, $df = 1$, $p<2.2\text{x}10^{-16}$) (Table 2). The average number of SGAs used trended upward from 1.1 to 1.3 (Table 2). The rate of SGA monotherapy use was in 2001, 2006, 2011, 2016 and 2021 were only 9.1%, 16.3%, 18.9%, 23.2% and 29.3%, respectively, but there was an increasing trend over the past 20 years ($\chi2 = 32.3$, $df = 1$, $p = 1.3\text{x}10^{-8}$) was observed (Fig 1). The complete monotherapy rates for SGAs without other psychotropic medications in 2001, 2006, 2011, 2016 and 2021 were only 0.7%, 2.7%, 3.5%, 5.0% and 6.3%, respectively, but the rates showed an increasing trend over the past 20 years ($\chi2 = 37.6$, $df = 1$, $p = 8.9\text{x}10^{-10}$) (Fig 1). On the other hand, the rate of FGA use in 2021 was 54.8%, and a decreasing trend was observed over the past 20 years. The average number of FGAs used trended downward, from 1.9 to 1.4 (Table 2).

Trend of dose of antipsychotics

In 2021, the average daily dose of SGAs prescribed to the patients was 558.8 mg (CPeq), and the average dose per person administered in the past 20 years showed a significant difference ($F = 123.1$, $df = 4$, $p = 2.5\text{x}10^{-82}$), with an increasing trend ($r = 0.950$, $p = 0.013$) (Table 2 and Fig 2). On the other hand, FGAs were prescribed to the patients in 2021 at an average daily dose of 230.0 mg of CPeq, and the average daily dose of CPeq per person receiving these drugs in the past 20 years was significantly different ($F = 103.4$, $df = 4$, $p = 4.6\text{x}10^{-97}$), showing a downward trend ($r = -0.984$, $p = 0.002$) (Table 2 and Fig 2). The mean daily CPeq dose of all antipsychotics prescribed to the patients in 2021 was 531.2 mg, which was unchanged

(F = 2.24, df = 4, p = 0.062) over the past 20 years (Fig 2). The average daily dose of anticholinergics (r = -0.994, p = 6.2×10^{-4}) and anxiolytics and sleeping pills (r = -0.931, p = 0.021) showed a decreasing trend over the past 20 years (Fig 2). The average daily dose of antidepressants was also unchanged (r = 0.865, p = 0.058) (Fig 2).

SGAs prescribed in 2001, 2006, 2011, 2016, and 2021 showed an increasing trend in the average daily dose for the patients (Fig 2); on the other hand, FGAs prescribed in these years showed a downward trend in the average daily CPeq dosage for the patients (Fig 2). The average daily CPeq dosage of patients prescribed any antipsychotic remained constant over the past 20 years (Fig 2). Ratios of FGA CPeq dose to antipsychotic total CPeq dose showed a decreasing trend over the past 20 years, while those of SGA CPeq dose to antipsychotic total CPeq dose showed a increasing trend over the past 20 years (Fig 3).

Trend of concomitant psychotropic agents

On the other hand, the rates of concomitant use of anticholinergics, antidepressants, anxiolytics/sleep medications and mood stabilizers in 2021 were 57.4%, 8.2%, 66.1%, and 21.9%, respectively (Table 2). The frequency of anticholinergic use differed over the 20 years (Cochran Q = 261.8, df = 4, p = 1.88×10^{-55}), with a decreasing trend over the past 20 years ($\chi 2$ = 133.4, df = 1, p<2.2×10^{-16}) (Table 2). The antidepressants used were also unchanged (Cochran Q = 1.57, df = 4, p = 0.820) (Table 2). The frequencies of anxiolytic and sleeping pill use differed over the 20 years (Cochran Q = 15.2, df = 4, p = 0.04), but without any trend over the 20 years ($\chi 2$ = 4.86, df = 1, p = 0.028) (Table 2). The mood stabilizers used differed over the 20 years (Cochran Q = 23.6, df = 4, p = 9.75×10^{-5}), but without any trend over the past 20 years ($\chi 2$ = 1.82, df = 1, p = 0.177) (Table 2).

Factor associating SGA use

In a multivariate analysis using age and gender as covariates, monotherapy use of SGA and SGA ratio in all antipsychotics in 2021 were significantly correlated with the presence or absence of hospitalization (Table 3).

Discussion

This study is the first in the world to follow the same patients with schizophrenia for 20 years in terms of the antipsychotics prescribed. The results of this study showed a slow but steady substitution of FGAs for SGAs over time. In addition, the rate of FGA monotherapy prescription decreased, whereas the rate of SGA monotherapy prescription gradually increased, but by less than half. The fact that SGA prescription has become mainstream since 2016, although this study did not incorporate new patients and the study population was not likely to take SGAs, may be due to the guidelines and other educational activities. This result is particularly positive even in Japan, a conservative country that favors multidrug therapy. In addition, although the dosage of the antipsychotics did not change, ratio of SGAs to FGA dose was clearly elevated. This suggests that even if FGA were used in combination with SGA, the dosage would be kept small. Furthermore, this result is a corollary of the fact that SGA has replaced FGA as the mainstay of treatment, even for the same patients, over the past two decades.

A history of previous hospitalization was identified as a factor for switching to SGA. This is an understandable result, because it is safer to switch medications during hospitalization. Since there are still a certain number of outpatients treated with FGAs, it is necessary to develop a method to safely switch to SGAs in the outpatient setting in the future.

Although guidelines recommend monotherapy with antipsychotics, the most frequently chosen treatment strategy internationally was combination antipsychotic therapy, prescribed in 49% of all patients.[7,21] Combination antipsychotic therapy is recommended only as a last resort when clozapine has not been successful,[22,23] although the use rate of clozapine is low in Japan.[24] Despite these recommendations, adjunctive treatment strategies are often used in schizophrenia before trial of clozapine.[25] Combination antipsychotic therapy is prescribed to 10-20% of outpatients, and as many as 50% of inpatients require two or more antipsychotics.[26]Another study showed that combination antipsychotic therapy is prescribed to 10-20% of outpatients, and as many as 50% of inpatients require two or more antipsychotics. Furthermore, a study

reported that combination therapy was prescribed to 42.5% of patients and augmentation therapy to 70% of patients.[27]Combination therapy for schizophrenia in the "real world" may be aimed at enhancing the efficacy of antipsychotics and reducing side effects by utilizing the different receptor binding profiles of various medications.

The results of this study showed lower SGA and monotherapy rates than the results of other cross-sectional studies. The results of comparisons of combination antipsychotic therapy with monotherapy remain controversial. Combination antipsychotic therapy has shown little evidence of superior efficacy[28,29] and is associated with a cumulative risk of adverse effects,[30]pharmacokinetic interactions, mortality[31] and increased costs compared with monotherapy.[32]

In the EGUIDE study of hospitalized patients in Japan, an analysis of the prescription rate from 2017 to 2019 showed a 90% SGA prescription rate and a 50% SGA monotherapy prescription rate.[33]On the other hand, in the REAP study,[34] which focused on outpatients, there was a significant decrease in the prescription rate of high-dose antipsychotics between 2001 and 2004, along with a decrease in the total daily dose of antipsychotics. In an international comparative pharmacoepidemiological study, overall rates of concomitant use of antipsychotics were shown to have declined over the past 20 years in Asia and to have slightly declined over the past 10 years in Europe.[12] Nevertheless, the concomitant use rate was much higher in Asia and Europe than in other Western countries. This may be partly related to the fact that in Eastern traditional medicine, mixtures of different medicinal ingredients are believed to be superior to single compounds.[35] On the other hand, the introduction of SGAs may have led to a decrease in concomitant use of antipsychotics, as concomitant use of FGAs was replaced with SGA monotherapy because of the expected or actual improved efficacy of SGAs.

Because concomitant use of anticholinergic drugs has been associated with many problems in cognitive function and peripheral side effects, such as constipation and urinary retention,[36,37] the guidelines recommend that anticholinergic drugs should not be used in combination. In this study, the results showed that the concomitant use rate and the average dosage used have gradually decreased over a period of 20 years. This finding may reflect the increasing use of SGAs, which have fewer extrapyramidal side effects, in addition to the widespread use of guidelines.

On the other hand, concomitant use of antidepressants increased even though antidepressants are not recommended by the guidelines. The addition of antidepressants to antipsychotic therapy for the treatment of schizophrenia is rather routine in clinical practice,[38] but evidence on the efficacy of antidepressants is still limited and inconsistent.[39] A recent comparative effectiveness study using U.S. Medicaid national data found a reduced risk of psychiatric hospitalization and emergency room visits among outpatients with schizophrenia who were prescribed adjunctive antidepressants.[40] In a recent meta-analysis, concomitant use of antidepressants proved to be partially effective.[12] Another factor may be that the widespread use of mirtazapine, which is less likely to cause side effects, instead of antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), which are more likely to cause activation syndrome, has reduced concerns about the concomitant use of antidepressants.

The prescribing rate of benzodiazepines did not change in this study. A recent systematic review did not test the efficacy of concomitant use of benzodiazepines with antipsychotics.[41] Furthermore, a recent meta-analysis of 16 randomized controlled trials confirmed the lack of efficacy data.[42] Therefore, in various guidelines, benzodiazepines were recommended for very short-term sedation of acutely agitated patients but not as an augmentation to antipsychotic therapy in the medium- to long-term pharmacotherapy of patients with schizophrenia and related disorders.

In a recent review, Carton et al. estimated that 40-75% of all antipsychotic prescriptions are for off-label use.[43]Mood disorders, anxiety disorders insomnia, and agitation were the main indications for antipsychotic use. A study in primary care in the United Kingdom found that a significant proportion of people prescribed antipsychotics had no record of psychosis or bipolar disorder, i.e., the "classic" indications for antipsychotics.[44] Similarly, only approximately 30% of antipsychotic prescriptions in Belgium were for psy-

chotic disorders.[45] In addition, a recent study of elderly patients in Taiwan suggested that approximately 80% of atypical antipsychotic users had a psychotic disorder, but only approximately 20% of typical antipsychotic users had a psychotic disorder. Only approximately 20% of atypical antipsychotic users had underlying psychiatric disorders.[46] On the other hand, in our study, only schizophrenia was evaluated, the patients were followed in one hospital for 20 consecutive years, and the diagnosis and prescriptions were confirmed by their attending physicians. The findings from our study are more reliable than those of studies that include many patients that use antipsychotics for other psychiatric disorders.

There are several limitations to this study. First, our study looked at prescribing rates every 5 years; therefore, we cannot rule out the possibility that prescribing rates may have changed during the 5-year intervals. We also cannot rule out the possibility that the prescriptions were switched during that time. It is common in practice for patients to request to return to their original medications due to side effects after attempting to change to different medications. Second, in this study, we did not evaluate symptoms over a 20-year period. Therefore, the causal relationship between the reason for change and the change in prescription cannot be clarified because it is unclear whether the change in prescription was due to unchanged symptoms or side effects. Finally, there is a bias in that patients who were transferred to other hospitals or died during the 20-year study period were not tracked, which is called panel mortality. In addition, this study was retrospective in design, whereas in the majority of published studies, panel studies were performed prospectively. The retrospective design of the study was because only the past trends in prescribing rates were investigated. In the future, prospective trend studies and cohort studies are necessary.

Conclusion

The results of this study showed a slow but steady substitution of SGAs for FGAs over time, even in the same patients. However, monotherapy of SGA has remained low, albeit with a slight upward trend. The rates of concomitant use of anticholinergics decreased, but those of antidepressants, and anxiolytics/sleep medications, and mood stabilizers were unchanged.

Acknowledgements

We thank Mr. Kazuyoshi Kawai for his invaluable assistance.

Conflict of interest statement

None.

Funding information

This research received no specific grant from any funding agencies in the public, commercial or not-for-profit sectors.

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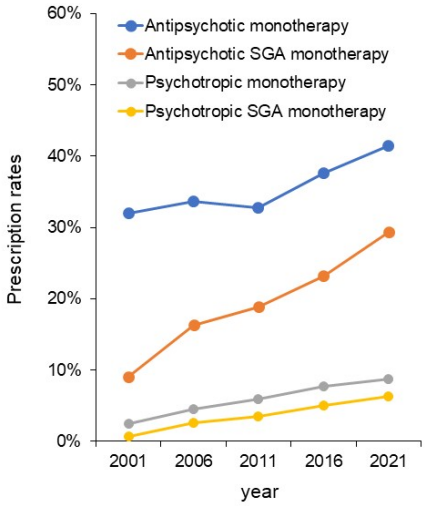
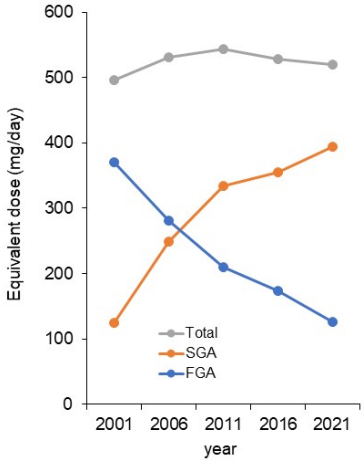
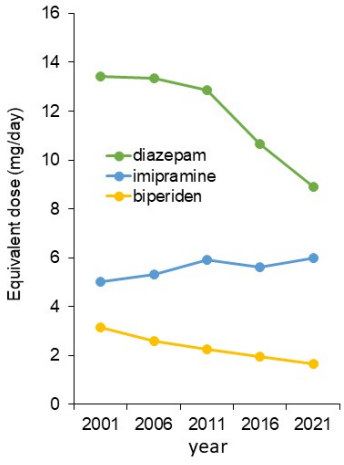
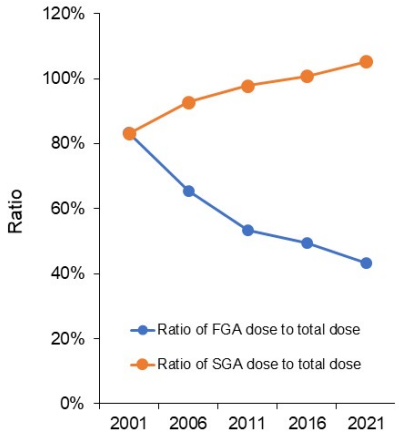
Figure legends Fig 1. These broken lines show the trend of the prescription rate of antipsychotics over time. Blue indicates monotherapy prescription rates for antipsychotics, orange indicates monotherapy prescription rates for second-generation antipsychotics (SGAs), gray indicates complete monotherapy use of psychotropic drugs, and yellow indicates complete monotherapy use of SGAs. Fig 2. The figure on the left shows the trend of chlorpromazine equivalent doses over time. Gray indicates doses of all antipsychotics, blue indicates doses of first-generation antipsychotics (FGA), and orange indicates doses of second-generation antipsychotics (SGA). The figure on the right shows the trend of equivalent doses of psychotropic drugs other than antipsychotics over time. Green indicates diazepam-equivalent doses of benzodiazepines, blue indicates imipramine-equivalent doses of antidepressants, and yellow indicates biperiden-equivalent doses of anticholinergics. Fig 3. This figure shows the trend over time of the percentage of first-generation antipsychotics (blue) and second-generation antipsychotics (orange) to chlorpromazine equivalent doses for

all antipsychotics.









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