CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
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# A survey of antipsychotic polypharmacy in outpatients at Nagoya University Hospital

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## ABSTRACT

**Purpose:** Antipsychotic polypharmacy has been utilized frequently in the clinical setting despite lack of evidence for its safety or efficacy. In an effort to promote the optimal use of antipsychotic medication, we examined the current state of antipsychotic polypharmacy and the use of excessive doses in outpatients with schizophrenia.
**Method:** The subjects of this study were schizophrenia patients who received oral antipsychotic medications from 1997 to 2007. The patient characteristics and prescription profiles, as well as the dosages, for all medications were obtained from the patients' medical charts. Psychotropic medications were classified into five categories: antipsychotics, antiparkinsonian agents, anxiolytics/sedative hypnotics, antidepressants, and mood stabilizers. The frequency of use and the equivalent doses of each psychotropic drug were summarized and used for correlation analysis. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine.
**Results:** Sixty-four percent of patients on antipsychotic pharmacotherapy received a single antipsychotic drug, and 36% received two or more. Among the 527 patients on monotherapy, 53.5% were prescribed first-generation antipsychotics (FGAs) and 46.5% were prescribed second-generation antipsychotics (SGAs) in the period from 1997 through 2007. Positive correlations between antipsychotics and antiparkinsonian agents were obtained both for the number of drugs ($p < 0.01$) and the equivalent dosage ($p < 0.01$); the prescribing rate for antiparkinsonian agents, however, fell significantly from 1997 to 2007 ($p < 0.0001$).
**Discussion:** These results suggest that the frequency with which antiparkinsonian agents are combined has also decreased due to the increase in the rate at which SGAs are prescribed. Greater awareness among psychiatrists at Nagoya University Hospital of the proper use of antipsychotics has resulted in a reduced prevalence of antipsychotic polypharmacy and less frequent use of excessive dosages.

***Keywords: antipsychotic polypharmacy, first generation antipsychotics, schizophrenia, second generation antipsychotics***

Received May 19, 2010 / Accepted July 15, 2010 / Published October 1, 2010

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## INTRODUCTION

Antipsychotic combination therapy, also called antipsychotic polypharmacy, has been utilized frequently in the clinical setting. The use of excessive doses, doses exceeding the optimal daily dose of 300 to 1000 mg in terms of chlorpromazine equivalents [1], are known to be involved in antipsychotic polypharmacy [2]. Polypharmacy and the use of excessive doses are widely prevalent (seen in approximately 10% to 50% of all patients) in the clinical setting in various countries [3-8], including Asian countries [9-11], despite evidence-based treatment guidelines that recommend the optimal prescription of antipsychotics -- that is, antipsychotic polypharmacy only after the failure of multiple monotherapies [12, 13]. Antipsychotic polypharmacy also remains controversial because of concerns about its possible adverse events [14], long-term safety [15, 16], excessive mortality [17, 18], increased cost [19, 20], and decreased adherence [21], as well as because of insufficient evidence supporting its efficacy [20, 22]. The introduction of second-generation antipsychotics (SGAs) in Japan [23] has resulted in a shift toward antipsychotic monotherapy in the clinical setting; on the other hand, SGAs are prescribed less often by Japanese psychiatrists than their US counterparts [24], and the problem of antipsychotic polypharmacy persists [10, 25].

In the present study, we examined the current state of antipsychotic polypharmacy in outpatients with schizophrenia at Nagoya University Hospital, in order to determine optimal antipsychotic medication prescription protocols.

## MATERIALS AND METHODS

All the outpatients with schizophrenia who received oral antipsychotic medications from 1997 to 2007 were included in the present study [term of the study: 1997 (1-3, 6-7 October), 2003 (1-3, 6-7 October), 2005 (1, 4-7 July), 2007 (4-8 June)]. The diagnoses were made by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Patient characteristics and prescription profiles for all medications, as well as the doses thereof, were obtained from the patients' medical charts.

The psychotropic medications were classified into five categories: antipsychotics (FGAs and SGAs), antiparkinsonian agents, anxiolytics/sedative hypnotics, antidepressants, and mood stabilizers, and their doses were converted into dose equivalents (except for mood stabilizers) in accordance with the dose equivalent calculation method of Inagaki et al. (2006) [26]: chlorpromazine equivalents (CPZ-eq), biperiden equivalents (BIP-eq), diazepam equivalents (DAP-eq), and imipramine equivalents (IMP-eq), respectively. The doses of drugs that were used for the treatment of symptoms other than core schizophrenia symptoms were excluded from this study.

We utilized the following statistical methodologies: Student's t-test for the mean scores, chi-squared tests for the categorical data, and Spearman's correlation analysis for the analysis of prescribing trends during the term of the study. All tests were two-tailed with significance levels of 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences, Version 11.0.

This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine. Researchers collected patient information from the subjects' medical charts without identifying them.

## RESULTS

Patient characteristics are shown in Table 1. The age distribution was wide (6-89 years), with a mean age of 28.1±15.7 years. By gender, the distribution was skewed towards females (55.4%), with the female dominance being consistent across all age groups ($\chi^2 = 2.58$, d.f. = 3, $p = 0.459$).

**Table 1. Patient characteristics (N = 827)**

| | 1997[a] | 2003 | 2005 | 2007 | Total |
|---|---|---|---|---|---|
| Male (%) | 58 (42.6) | 92 (41.6) | 120 (48.6) | 99 (44.4) | 369 (44.6) |
| Female (%) | 78 (57.4) | 129 (58.4) | 127 (51.4) | 124 (55.6) | 458 (55.4) |
| Age[b] | 40.4±14.4 (12-71) | 37.6±15.3 (7-70) | 36.0±15.4 (6-71) | 39.7±17.1 (7-89) | 38.1±15.7 (6-89) |

[a] Term of the study: 1997 (1-3, 6-7 October), 2003 (1-3, 6-7 October), 2005 (1, 4-7 July), 2007 (4-8 June)

[b] Age: mean±standard deviation

The psychotropic drug trends are summarized in Table 2. The frequency of use of each type of psychotropic drug was consistent during the term of the study (1997-2007). The rates with which FGAs and antiparkinsonian agents were prescribed decreased ($\chi^2$ = 143.0, d.f. = 3, p < 0.0001 and $\chi^2$ = , d.f. = 3, p < 0.0001, respectively), while the rates with which SGAs and mood stabilizers were prescribed increased ($\chi^2$ = 187.8, d.f. = 3, p < 0.0001 and ($\chi^2$ = 15.1, d.f. = 3, p < 0.01, respectively). Among patients on antipsychotic pharmacotherapy, 64% received a single antipsychotics (monotherapy), and 36% received two or more antipsychotics (polypharmacy). Among the 527 patients on monotherapy in 1997 to 2007, 53.5% were prescribed FGAs and 46.5% were prescribed SGAs.

**Table 2. Prescription profiles (N = 827)**

| | 1997[a] | 2003 | 2005 | 2007 | Total |
|---|---|---|---|---|---|
| Number of drugs: mean±SD[b] (min[c]-max[d]) | | | | | |
| Antipsychotics | 1.6±0.9 (1-5) | 1.6±0.8 (1-4) | 1.4±0.7 (1-4) | 1.4±0.7 (1-5) | 1.5±0.8 (1-5) |
| Antiparkinsonian agents | 0.7±0.6 (0-3) | 0.5±0.6 (0-2) | 0.4±0.6 (0-2) | 0.3±0.5 (0-2) | 0.4±0.6 (0-3) |
| Anxiolytics/sedative-hypnotics | 1.2±1.2 (0-7) | 1.6±1.3 (0-6) | 1.4±1.2 (0-6) | 1.3±1.2 (0-6) | 1.4±1.2 (0-7) |
| Antidepressants | 0.3±0.7 (0-3) | 0.5±0.8 (0-3) | 0.5±0.7 (0-5) | 0.4±0.6 (0-3) | 0.4±0.7 (0-5) |
| Mood stabilizers | 0.1±0.4 (0-2) | 0.2±0.4 (0-1) | 0.2±0.4 (0-2) | 0.3±0.5 (0-2) | 0.2±0.4 (0-2) |
| Prescription rate (%) | | | | | |
| Antipsychotics | | | | | |
| FGA[e]-user | 97.8 (133/136) | 80.5 (178/221) | 61.5 (152/247) | 42.2 (94/223) | 67.4 (557/827) |
| SGA[f]-user | 6.6 (9/136) | 40.7 (90/221) | 57.5 (142/247) | 78.5 (175/223) | 50.3 (416/827) |
| Monotherapy[g] | 57.4 (78/136) | 60.2 (133/221) | 66.0 (163/247) | 68.6 (153/223) | 63.7 (527/827) |
| FGA only | 96.2 (75/78) | 70.7 (94/133) | 46.0 (75/163) | 24.8 (38/153) | 53.5 (282/527) |
| SGA only | 3.8 (3/78) | 29.3 (39/133) | 54.0 (88/163) | 75.2 (115/153) | 46.5 (245/527) |
| Polypharmacy[h] | 42.6 (58/136) | 39.8 (88/221) | 34.0 (84/247) | 31.4 (70/223) | 36.3 (300/827) |
| FGA / FGA | 89.7 (52/58) | 42.0 (37/88) | 35.7 (30/84) | 14.3 (10/70) | 43.0 (129/300) |
| SGA / SGA | 0 (0/58) | 4.5 (4/88) | 7.1 (6/84) | 20.0 (14/70) | 8.0 (24/300) |
| FGA / SGA | 10.3 (6/58) | 53.4 (47/88) | 57.1 (48/84) | 65.7 (46/70) | 49.0 (147/300) |
| Antiparkinsonian agents | 61.8 (84/136) | 43.0 (95/221) | 32.8 (81/247) | 28.3 (63/223) | 39.1 (323/827) |
| Anxiolytics/sedative-hypnotics | 66.2 (90/136) | 75.6 (167/221) | 75.3 (186/247) | 69.5 (155/223) | 72.3 (598/827) |
| Antidepressants | 25.0 (34/136) | 33.5 (74/221) | 38.9 (96/247) | 32.3 (72/223) | 33.4 (276/827) |
| Mood stabilizers | 10.3 (14/136) | 16.3 (36/221) | 18.2 (45/247) | 26.0 (58/223) | 18.5 (153/827) |
| Equivalent dosage: eq[i] mg±SD (min-max) | | | | | |
| Antipsychotics: CPZ[j]-eq | 293.3±315.7 (10.0-1963.6) | 271.7±366.0 (2.5-3000.0) | 272.4±305.8 (5.0-1500.0) | 327.9±333.5 (12.5-1450.0) | 290.6±332.1 (2.5-3000.0) |
| < 600mg (%) | 88.2 (120/136) | 88.2 (195/221) | 85.8 (212/247) | 82.1 (183/223) | 85.9 (710/827) |
| 600-999mg (%) | 6.6 (9/136) | 6.3 (14/221) | 8.1 (20/247) | 10.8 (24/223) | 8.1 (67/827) |
| 1000mg ≦ (%) | 5.1 (7/136) | 5.4 (12/221) | 6.1 (15/247) | 7.2 (16/223) | 6.0 (50/827) |
| Antiparkinsonian agents: BIP[k]-eq | 2.0±2.2 (0.0-9.0) | 1.4±2.0 (0.0-12.0) | 1.0±1.8 (0.0-12.0) | 0.7±1.4 (0.0-9.0) | 1.2±1.9 (0.0-12.0) |
| Anxiolytics/sedative-hypnotics: DAP[l]-eq | 13.2±20.2 (0.0-125.0) | 16.2±19.1 (0.0-188.0) | 13.4±19.6 (0.0-240.0) | 12.7±18.4 (0.0-170.0) | 13.9±19.2 (0.0-240.0) |
| Antidepressants: IMP[m]-eq | 23.3±52.2 (0.0-275.0) | 41.2±77.8 (0.0-497.5) | 44.5±81.7 (0.0-525.0) | 39.0±77.7 (0.0-612.5) | 38.7±75.6 (0.0-612.5) |

[a] Term of the study: 1997 (1-3, 6-7 October), 2003 (1-3, 6-7 October), 2005 (1, 4-7 July), 2007 (4-8 June)

[b] SD: standard deviation, [c] min: minimum, [d] max: maximum

[e] FGA: first-generation antipsychotics, [f] SGA: second-generation antipsychotics

[g] Monotherapy: medication by single (one) antipsychotic drug, [h] Polypharmacy: multiple (two or more) use of antipsychotics

[i] eq: equivalent, [j] CPZ: chrolpromazine, [k] BIP: biperiden, [l] DAP: diazepam, [m] IMP: imipramine

The proportion of patients on SGA monotherapy increased consistently across the term of the study ($\chi^2 = 127.0$, d.f. = 3, $p < 0.0001$). Of the patients who were prescribed two or more antipsychotics, 43.0% received only FGAs (FGA/FGA), 8.0% received only SGAs (SGA/SGA), and 49.0% received combinations of FGAs and SGAs (FGA/SGA). The proportion of patients receiving FGA/FGA polypharmacy decreased during the term of the study, while SGA polypharmacy (both SGA/SGA and FGA/SGA) tended to increase ($\chi^2 = 76.9$, d.f. = 3, $p < 0.0001$).

The antipsychotic equivalent doses (CPZ-eq) decreased form 1997 to 2003; however, this trend changed in 2007, as the dosages were increased. Approximately 85% of subjects were within the optimal dose range at each study period (1997, 2003, 2005, and 2007). The BIP-eq dose decreased significantly, the DAP-eq dose did not vary, and the IMP-eq dose increased from 1997 to 2007. Significantly higher doses of antipsychotics were prescribed to the polypharmacy group (471.1 ± 388.1 mg CPZ-eq) than to patients who were on a single antipsychotic drug in both the FGA (120.2 ± 236.0) and SGA (251.2 ± 208.7) groups ($F = 104.5$, d.f. = 2, $p < 0.0001$).

Table 3 shows the results of correlation analysis of the numbers and equivalent doses of psychotropic medications. Positive correlations were observed between FGAs and antiparkinsonian agents and anxiolytics/sedative hypnotics, but no correlations were observed between SGAs and antiparkinsonian agents or anxiolytics/sedative hypnotics. A negative correlation was observed between antidepressants and antiparkinsonian agents, and a positive correlation was observed between antidepressants and anxiolytics/sedative hypnotics. A positive correlation was observed between mood stabilizers and SGAs. Looking at the equivalent doses, a positive correlation was seen between antipsychotics and antiparkinsonian agents, and a negative correlation was observed between antipsychotics and antidepressants. A weak positive correlation was observed between FGAs and anxiolytics, but no correlations were observed between SGAs and drugs other than antidepressants. A negative correlation was observed between antidepressants and antiparkinsonian agents, and a positive correlation was observed between antidepressants and anxiolytics/sedative hypnotics. The strongest correlation for the number of drugs and the equivalent dose was observed between antipsychotics and antiparkinsonian agents [r = 0.396 (FGAs: r = 0.348), r = 0.451 (FGAs: r = 0.449), respectively].

**Table 3. Correlation analysis of psychotropic medications for the number of drugs and equivalent dosages (N = 827)**

| | Antipsychotics | FGAs | SGAs | Antiparkinsonian agents | Anxiolytics/ sedative-hypnotics | Anti-depressants | Mood stabilizers |
|---|---|---|---|---|---|---|---|
| Antipsychotics | 1 | **0.657**$^{**}$ | **0.170**$^{**}$ | **0.396**$^{**}$ | **0.104**$^{**}$ | **-0.100**$^{**}$ | **0.044** |
| First-generation antipsychotics (FGAs) | *0.176*$^{**}$ | 1 | **-0.589**$^{**}$ | **0.348**$^{**}$ | **0.092**$^{**}$ | **-0.004** | **-0.061** |
| Second-generation antipsychotics (SGAs) | *0.651*$^{**}$ | *-0.508*$^{**}$ | 1 | **-0.028** | **0.007** | **-0.075**$^{*}$ | **0.111**$^{**}$ |
| Antiparkinsonian agents | *0.451*$^{**}$ | *0.449*$^{**}$ | *0.053* | 1 | **0.005** | **-0.216**$^{**}$ | **0.002** |
| Anxiolytics/sedative-hypnotics | *0.022* | *0.092*$^{**}$ | *0.011* | *0.037* | 1 | **0.338**$^{**}$ | **0.009** |
| Antidepressants | *-0.209*$^{**}$ | *-0.081*$^{*}$ | *-0.081*$^{*}$ | *-0.190*$^{**}$ | *0.311*$^{**}$ | 1 | **-0.020** |

Spearman's correlation analysis (*p < 0.05, **p < 0.01)

**Bold numbers**: the correlation coefficients for the number of psychotropic medications

*Italic numbers*: the correlation coefficients for the equivalent dosages of psychotropic medications (excluding mood stabilizers)

## DISCUSSION

In the present study, the antipsychotic monotherapy rate increased from 57.4% (1997) to 68.6% (2007), and the number of drugs slightly decreased from 1.6 ± 0.9 (1997) to 1.4 ± 0.7 (2007), although the decrease was not significant. Previous analyses of prescription patterns revealed that the antipsychotic monotherapy rate was 22.6% in 1995, 45.1% in 2002, and 49.0% in 2005, and that the mean number of drugs was 1.8 ± 1.0 in 2005 [27]. Our results revealed a higher monotherapy rate and a lower number of drugs than previous studies, suggesting that improved awareness among psychiatrists has resulted in greater use of antipsychotic monotherapy. The mean CPZ-eq was approximately 300 mg/day during the term of the study, which is within the recommended dosage range (acute phase: 300 to

1000 mg/day; chronic phase: 300 to 600 mg/day) [1], and thus appears to follow antipsychotic use recommendations. Furthermore, although the prescribing rate of SGAs was initially (until 2003) less than 30%, which was much lower than in other countries, subsequent dramatic changes in the antipsychotic therapies used for schizophrenia in the clinical setting resulted in a significant increase in this rate, to nearly 80%, by 2007. Accompanying the shift in schizophrenia treatment (towards SGAs) over the past ten-odd years [24], the FGA/FGA polypharmacy prescription rate decreased from 1997 to 2007. However, the prevalence of SGA (SGA/SGA or FGA/SGA) polypharmacy increased substantially. These findings are consistent with previously reported results [24, 28, 29]. SGAs were marketed as offering greater efficacy in improving psychotic symptoms while reducing side effects [especially extrapyramidal symptoms (EPS)] compared to FGAs [30]. FGA/SGA polypharmacy has been shown to result in a higher incidence of EPS than FGA monotherapy [2]. Correlation analyses revealed a positive correlation between antipsychotics and antiparkinsonian agents in both the number of drugs and the equivalent doses (Table 3). The antiparkinsonian agent prescription rate has significantly decreased ($p < 0.0001$), suggesting that the frequency with which antiparkinsonian agents are combined with other drugs has also decreased due to the increased SGA prescription rate. The fact that anxiolytics/sedative hypnotics correlated only with FGAs suggests that the shift towards the use of SGAs and the less frequent use of FGA/FGA polypharmacy will result in less frequent concomitant use of anxiolytics/sedative hypnotics with antipsychotics. Several significant correlations were also detected: between SGAs and mood stabilizers (positive), antidepressants and antipsychotics (negative), and antidepressants and antiparkinsonian agents (negative). In other words, according to our data, SGAs could not control mood oscillation in schizophrenia, so mood stabilizers might be used to compensate for the weak sedative effect of SGAs. Furthermore, the negative correlation between antipsychotics and antidepressants might indicate a nonspecific dose-dependent antipsychotic antidepressant effect, while the negative correlation between antidepressants and antiparkinsonian agents is just a collateral effect that reflects the use of higher doses of antipsychotics.

**Supplementary Table 1. Correlation analysis of psychotropic medications for the number of drugs and equivalent dosages in adults (N = 663)**

| | Antipsychotics | FGAs | SGAs | Antiparkinsonian agents | Anxiolytics/ sedative-hypnotics | Anti-depressants | Mood stabilizers |
|---|---|---|---|---|---|---|---|
| Antipsychotics | 1 | **0.687**$^{**}$ | **0.142**$^{**}$ | **0.394**$^{**}$ | **0.057** | **-0.119**$^{**}$ | **0.044** |
| First-generation antipsychotics (FGAs) | *0.187*$^{**}$ | 1 | **-0.579**$^{**}$ | **0.336**$^{**}$ | **0.032** | **-0.016** | **-0.052** |
| Second-generation antipsychotics (SGAs) | *0.646*$^{**}$ | *-0.508*$^{**}$ | 1 | **-0.006** | **0.039** | **-0.080**$^{*}$ | **0.100**$^{**}$ |
| Antiparkinsonian agents | *0.466*$^{**}$ | *0.444*$^{**}$ | *0.065* | 1 | **-0.030** | **-0.244**$^{**}$ | **0.008** |
| Anxiolytics/sedative-hypnotics | *-0.027* | *0.040* | *0.011* | *0.000* | 1 | **0.341**$^{**}$ | **0.009** |
| Antidepressants | *-0.246*$^{**}$ | *-0.103*$^{**}$ | *-0.089*$^{*}$ | *-0.222*$^{**}$ | *0.305*$^{**}$ | 1 | **-0.020** |

Spearman's correlation analysis (*$p < 0.05$, **$p < 0.01$)

**Bold numbers**: the correlation coefficients for the number of psychotropic medications

*Italic numbers*: the correlation coefficients for the equivalent dosages of psychotropic medications (excluding mood stabilizers)

Several limitations need to be considered in order to interpret the present findings. Firstly, the diagnoses were made by a psychiatrist based solely on the DSM-IV criteria. Structured interviews with patients and families and a review of the medical records should be considered in order to exclude other neuropsychiatric disorders, such as mood disorders, personality disorders, obsessive-compulsive disorders, and neurodevelopmental disorders. Secondly, previous studies suggest that confounding factors related to polypharmacy and excessive dosing might include sampling biases, patient factors such as age and clinical measures (e.g., psychopathology and severity and duration of illness), health care provider factors, such as knowledge of pharmacology, the local culture, clinical experience, and familiarity with the literature [25]. In general, stratification by age (children and the elderly as one group and adults as another group) might be a confounding factor due to possible treatment differences. The results of the

correlation analysis without children (age < 20 years) or the elderly (age > 64 years) yielded results similar to those of the analysis conducted using all participants (Supplementary Table 1), suggesting that patient age is not a factor that affects the present results. Despite the aforementioned or other considerations, our results revealed shifting antipsychotic polypharmacy prescription patterns and a trend towards excessive doses between 1997 and 2007.

In conclusion, greater awareness among psychiatrists at Nagoya University Hospital of the proper use of antipsychotics has resulted in a reduced prevalence of antipsychotic polypharmacy and less frequent use of excessive dosages. Further investigations should focus on the relationship between prescribing patterns and the long-term outcomes of patients, such as quality of life (QOL) and satisfaction with antipsychotic medication, in order to obtain clinical insights into the optimal use of antipsychotic medications.

## ACKNOWLEDGEMENTS

We sincerely thank the patients for their participation in our study.

## CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

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