

# Antipsychotic Medications in Major Depression and the Association with Treatment Satisfaction and Quality of Life: Findings of Three National Surveys on Use of Psychotropics in China Between 2002 and 2012

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## Abstract

**Background:** Optimizing treatment outcomes for depression requires understanding of how evidence-based treatments are utilized in clinical practice. Antipsychotic medications concurrent with antidepressant treatment are frequently used in major depression, but few studies have investigated trends and patterns of their use over time. This study aimed to examine the prescription patterns of antipsychotic medications for major depression in China from 2002 to 2012 and their association with treatment satisfaction and quality of life (QOL).

**Methods:** A total of 3655 subjects with major depression treated in 45 Chinese psychiatric hospitals/centers nationwide were interviewed between 2002 and 2012. Patients' socio-demographic and clinical characteristics including psychopathology, medication side effects, satisfaction with treatment and QOL were recorded using a standardized protocol and data collection.

**Results:** The frequency of antipsychotic use was 24.9% in the whole sample; the corresponding figures were 17.1%, 20.3%, and 32.8% in 2002, 2006, and 2012, respectively ( $\chi^2 = 90.3$ ,  $df = 2$ ,  $P < 0.001$ ). Multiple logistic regression analyses revealed that patients on concurrent antipsychotics had significantly more delusions or hallucinations, longer illness duration, greater side effects, and more likely to be treated as inpatients and in major hospitals (i.e., Level-III hospital). Antipsychotic use was associated with lower treatment satisfaction while there was no significant difference with respect to physical and mental QOL between the antipsychotic and nonantipsychotic groups.

**Conclusions:** Concurrent antipsychotic use was found in about one in four treated depressed patients in China, which has increased over a 10-year period. Considering the association of drug-induced side effects and the lack of patients' and relatives' satisfaction with antipsychotic treatment, further examination of the rationale and appropriateness of the use of antipsychotics in depression is needed.

**Key words:** Antipsychotic Medication; Major Depression; Prescription Patterns

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## INTRODUCTION

It is estimated that up to 50% of depressed patients either do not respond or only partially respond to an adequate course of antidepressant treatment.<sup>[1-3]</sup> Consequently,

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augmentation strategies have been commonly used in treating major depression.<sup>[4]</sup> Although the first generation antipsychotics (FGA) have been in use for treating major depression for a long time, their extrapyramidal side effects (EPS) have discouraged their use. Second generation antipsychotics (SGA) have become widespread in depression in the past decade due to the lower risk for EPS.<sup>[5]</sup> A meta-analysis of sixteen trials with 3480 patients has found that SGAs are an effective augmentation treatment for major depression, but they are frequently discontinued due to adverse events.<sup>[4]</sup> The US Food and Drug Administration have already approved the use of olanzapine (in combination with fluoxetine), aripiprazole (5–10 mg/d, maximum dosage 15 mg/d), and quetiapine extended release (50–300 mg/d) as adjunctive agents for depression.<sup>[6]</sup> Most treatment guidelines recommend SGAs for augmentation in treating depression.<sup>[6]</sup>

Regular cross-sectional surveys of prescription patterns are an efficient and fast way of obtaining a global picture of pharmacotherapy practice in a given setting.<sup>[7]</sup> However, little is known about how antipsychotic medications are used over time in the treatment of depression in China where the mental health system is not only fundamentally different from other countries but has undergone rapid changes in the last decade. In a recent study of misdiagnosed bipolar patients receiving treatment for major depression, 19.2% of depressed Chinese patients received an antipsychotic drug.<sup>[8]</sup> As the study only involved 13 major psychiatric hospitals or units, its findings cannot be generalized. Furthermore, the impact of antipsychotics on important outcomes such as patients' and their families' satisfaction with treatment and quality of life (QOL) was not explored.

Thus, this study aimed to: (1) Examine the prescription patterns of antipsychotic medications for depression across China nationally from 2002 to 2012; and (2) to explore the demographic and clinical correlates of adjunctive antipsychotic treatment and the association with treatment satisfaction and QOL.

## METHODS

### Study design and participants

This was a cross-sectional nationwide pharmaco-epidemiological survey which was conducted in China initiated by the Chinese Society of Psychiatry. The first survey took place in May 2002 followed by another two surveys in May 2006 and July-August 2012 using the same design and standardized protocol. Consensus meetings on data collection and uniformity of data entry were held prior to each survey. A total of 45 psychiatric centers/units located in 10 provinces and municipalities including Beijing, Guangdong, Hebei, Hubei, Jiangxi, Jiangsu, Jilin, Shaanxi, Shanxi, and Sichuan participated in each survey. Districts were selected based on economic levels defined by the GDP report in 2000. The same 45 mental health centers/units were included in all the three surveys.<sup>[9,10]</sup>

One for every 14 inpatients and outpatients receiving treatment in the participating hospitals/units during the data

collection period of 4 weeks were consecutively referred by their treating psychiatrists to the research team to be screened for eligibility. All members of the research team were attending psychiatrist with at least 3-year working experience. Inclusion criteria included: (1) DSM-IV or ICD-10 diagnosis of major depressive disorder (MDD) based on a clinical interview and review of medical records; (2) age 15 years or older; (3) ability to understand the aims and the contents of the survey. Those with comorbid psychotic disorders were excluded.

The study protocol was approved by the Ethics Committees of the participating centers. All patients provided written informed consent.

### Assessments

Basic socio-demographic and clinical characteristics were collected using a form designed for the study. Information about the types and doses of psychotropic drugs were collected from the medical records.

Following the same procedures as in the Research on Asian Psychotropic Prescription project,<sup>[11,12]</sup> delusions, hallucinations, and suicidality in the past month were evaluated during the diagnostic interview. Global illness severity was evaluated with the Chinese version of the Clinical Global Impressions-Severity scale (CGI-S).<sup>[13]</sup> The Treatment Emergent Symptom Scale (TESS)<sup>[14]</sup> was used to record side effects. Patients and their families' satisfaction with the current treatment was evaluated with a self-rated, 7-point Likert scale, scoring from 1 (extreme dissatisfaction) to 7 (extreme satisfaction). QOL was assessed with the Chinese version of the Medical Outcomes Study Short Form 12 (SF-12).<sup>[15,16]</sup> The SF-12 is a multidimensional generic instrument with 12 items on physical and mental QOL domains. A higher score on SF-12 indicates better QOL.

In China, hospitals are classified into three levels according to the degree of specialization in clinical care and research. Level-III hospitals have the highest staff-patient ratio and medical resources while Level-II hospitals are regional medical centers that treat patients with severe diseases, and Level-I hospitals are small, community level hospitals providing basic medical care.<sup>[17]</sup> There was no Level-I psychiatric hospital at the study time in the areas included, thus only Level-III/II medical facilities were included in this study.

All the 135 raters were trained in the use of the above-mentioned instruments. The inter-rater reliability of the instruments conducted in 20 MDD patients prior to the study yielded satisfactory to good agreement (>0.75).

### Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago, IL, USA). In the pooled sample, comparisons between the antipsychotic and nonantipsychotic groups with respect to demographic and clinical variables

were conducted with Chi-square tests, independent-samples *t*-test or Mann–Whitney *U*-test, as appropriate. Multiple logistic regression analysis with the “enter” method (i.e., all specified independent variables were entered at one time) was used to determine the demographic and clinical variables that were independently and significantly associated with antipsychotic use. Antipsychotic prescription was the dependent variable, while variables that significantly differed between the two groups in univariate analyses were entered as independent variables.

Patients and their families’ satisfaction with the current treatment and QOL were only measured in the 2012 survey. In the 2012 sample, satisfaction with the current treatment and QOL were compared between the antipsychotic and nonantipsychotic groups after controlling for the potential confounding effects of variables that significantly differed between the two groups in univariate analyses using analysis of covariance (ANCOVA). Significance level was set at  $P < 0.05$  (two-tailed).

## RESULTS

A total of 4356 patients from 45 psychiatric hospitals/centers were screened for study entry; 3655 met the study criteria: 735 in 2002, 1389 in 2006, and 1531 in 2012, resulting in an overall participation rate of 83.9%.

The frequency of antipsychotic prescriptions was 24.9% (910/3655) in the whole sample; the corresponding figures were 17.1% (126/735) in 2002, 20.3% (282/1389) in 2006, and 32.8% (502/1531) in 2012 ( $\chi^2 = 90.3$ ,  $df = 2$ ,  $P < 0.001$ ). In the whole sample, the proportion of FGAs and SGAs was 6.1% (222/3655) and 19.4% (708/3655), respectively, with these figures being 12.4% (91/735) and

5.2% (38/735) in 2002, 6.9% (96/1389) and 14.2% (197/1389) in 2006, and 2.3% (35/1531) and 30.9% (473/1531) in 2012.

Table 1 shows the socio-demographic and clinical characteristics of the whole sample and those of the antipsychotic and nonantipsychotic groups. Table 2 displays the factors independently associated with antipsychotic prescription. Compared to the nonantipsychotic group, patients on antipsychotics had more delusions or hallucinations, significantly longer illness duration and higher TESS total score; were more likely to be inpatients and receive treatment in Level-III hospitals. These variables totally account for 26.9% of the variance of antipsychotic use ( $P < 0.001$ ).

Table 3 shows the socio-demographic and clinical characteristics, treatment satisfaction, and QOL in the 2012 sample, and separately according to antipsychotic prescription. After controlling for the potential confounding effects of variables that significantly differed between the two groups (inpatient status, presence of delusions or hallucinations and suicidality in the past month, hospital level, age of onset, duration of illness, and scores of CGI-S and TESS) using ANCOVA, antipsychotic use was associated with lower patients’ ( $F_{(9,1521)} = 12.4$ ,  $P < 0.001$ ) and family’s treatment satisfaction ( $F_{(9,1521)} = 11.1$ ,  $P = 0.001$ ), while there was no significant difference with respect to physical ( $F_{(9,1521)} = 1.7$ ,  $P = 0.18$ ) and mental QOL ( $F_{(9,1521)} = 0.6$ ,  $P = 0.42$ ).

Table 4 presents the frequently prescribed antipsychotic drugs across the three surveys. The first three most commonly prescribed antipsychotic drugs were sulpiride, perphenazine, and risperidone in 2002, olanzapine, risperidone, and quetiapine in 2006 and olanzapine, quetiapine, and risperidone in 2012.

**Table 1: Comparison between patients with or without adjunctive antipsychotic medication with respect to basic demographic and clinical variables during 2002–2012**

Variables	Total sample ( <i>n</i> = 3655)	Nonantipsychotics ( <i>n</i> = 2745)	Antipsychotics ( <i>n</i> = 910)	Statistics	df	<i>P</i>
Male sex, <i>n</i> (%)	1305 (35.7)	962 (35.0)	343 (37.7)	2.0 <sup>†</sup>	1	0.140
Inpatient, <i>n</i> (%)	1257 (34.4)	794 (28.9)	463 (50.9)	145.9 <sup>†</sup>	1	<0.001
Health insurance coverage, <i>n</i> (%)	1893 (51.8)	1348 (49.1)	545 (59.9)	31.8 <sup>†</sup>	1	<0.001
Family history of psychiatric disorders, <i>n</i> (%)	537 (14.7)	387 (14.1)	150 (16.5)	3.01 <sup>†</sup>	1	0.070
Delusions or hallucinations in the past month, <i>n</i> (%)	116 (3.2)	14 (0.5)	102 (11.2)	254.5 <sup>†</sup>	1	<0.001
Suicidality in the past month, <i>n</i> (%)	878 (24.0)	630 (23.0)	248 (27.3)	6.8 <sup>†</sup>	1	0.008
Hospital level, <i>n</i> (%)						
Level-II	1791 (49)	1377 (50.2)	414 (45.5)	5.9 <sup>†</sup>	1	0.010
Level-III	1864 (51)	1368 (49.8)	496 (54.5)			
On FGAs, <i>n</i> (%)	222 (6.1)		222 (24.4)			
On SGAs, <i>n</i> (%)	708 (19.4)		708 (77.8)			
Age (years, mean ± SD)	42.3 ± 14.9	42.1 ± 14.7	42.8 ± 15.3	-1.1 <sup>‡</sup>	3653	0.230
Age of onset (years, mean ± SD)	38.4 ± 14.3	38.6 ± 14.2	37.8 ± 14.6	1.4 <sup>‡</sup>	3653	0.770
Duration of illness (years, mean ± SD)	3.8 ± 5.8	3.5 ± 5.4	4.8 ± 6.9	-4.7 <sup>‡</sup>	—*	<0.001
CGI-S total (mean ± SD)	3.5 ± 1.4	3.5 ± 1.4	3.6 ± 1.3	-2.6 <sup>‡</sup>	—*	0.008
TESS total (mean ± SD)	0.8 ± 1.2	0.7 ± 1.0	1.1 ± 1.5	-7.4 <sup>‡</sup>	—*	<0.001

\*Mann–Whitney *U*-test; <sup>†</sup>Chi-square values. <sup>‡</sup>*t* values in independent-samples *t*-test or *Z* value in Mann–Whitney *U*-test. CGI-S: Clinical Global Impressions-Severity scale; FGAs: First generation antipsychotics; SGAs: Second generation antipsychotics; TESS: Treatment Emergent Symptom Scale; SD: Standard deviation.

## DISCUSSION

The major finding of this study is that the overall frequency of antipsychotic use in treated MDD patients in China was 24.9% in the 2002–2012 period, which is slightly higher than found in another multicenter survey (19.2%) in Chinese depressed patients.<sup>[8]</sup> The difference between the two studies may be due to the discrepancy in the number and types of institutions involved and diagnostic methods (a review of medical records and clinical interview versus the Mini International Neuropsychiatric Interview).

**Table 2: Factors associated with antipsychotic prescription in MDD (*n* = 910)**

Factors	<i>P</i>	<i>OR</i>	<i>95% CI</i>
Inpatient status	<0.001	2.3	1.9–2.8
Health insurance coverage	0.490	1.06	0.8–1.2
Delusions or hallucinations in the past month	<0.001	32.0	17.4–58.7
Suicidality in the past month	0.270	1.1	0.9–1.3
Level-III hospital	<0.001	1.6	1.3–2.0
Duration of illness (years)	<0.001	1.02	1.01–1.03
CGI-S total	0.780	1.01	0.9–1.1
TESS total	<0.001	1.3	1.2–1.4
Study time			
2002		1.0	
2006	0.016	1.3	1.1–1.8
2012	<0.001	2.6	2.0–3.4

Multiple logistic regression analysis with the nonantipsychotic group as the reference. Total  $R^2=0.269$ ,  $P<0.001$ . CGI-S: Clinical Global Impressions-Severity scale; TESS: Treatment Emergent Symptom Scale; *OR*: Odds ratio; *CI*: Confidence interval; MDD: Major depressive disorder.

Another significant finding is the increase of adjunctive antipsychotic drugs from 17.1% in 2002, 20.3% in 2006 and to 32.8% in 2012. This increase might possibly be explained by the increasing use of SGAs and decreasing use of FGAs at the same time, the recommendations of SGAs in treating depression in clinical guidelines and the growing impact of pharmaceutical companies over the past decade.

As expected, one fifth of patients received SGAs in the sample with increasing proportion over time (5.2% in 2002, 14.2% in 2006, and 30.9% in 2012) while the proportion of FGA use decreased over time: 6.1% in the whole sample and 12.4% in 2002, 6.9% in 2006, and 2.3% in 2012. We assume that a number of socio-economic factors including local psychopharmacological practice, prior antipsychotic treatment, uneven access to antipsychotic drugs, insurance coverage, and costs might all contribute to such use in Chinese MDD patients. Considering the risk of antipsychotic-induced EPS and the absence of a clearly documented rationale, the use of FGAs should be discouraged in this population.

Olanzapine was the most commonly used SGA in Chinese MDD patients (7.7%), followed by quetiapine (5.7%), risperidone (3.4%), and aripiprazole (0.8%) in the pooled sample during the period between 2002 and 2012. Such practice appears consistent with the US FDA approval of two SGAs – aripiprazole and extended release quetiapine – as adjunctive agents in antidepressant-resistant MDD in addition to olanzapine plus fluoxetine.<sup>[6]</sup> However, the response to antidepressants could not be measured in this cross-sectional survey. A meta-analysis has found that there were no significant differences in efficacy between

**Table 3: Comparison between the antipsychotic and nonantipsychotic groups with respect to basic demographic and clinical variables in 2012**

Variables	Total sample ( <i>n</i> = 1531)	Nonantipsychotics ( <i>n</i> = 1029)	Antipsychotics ( <i>n</i> = 502)	Statistics	df	<i>P</i>
Male sex, <i>n</i> (%)	537 (35.1)	357 (34.7)	180 (35.9)	0.2 <sup>†</sup>	1	0.650
Inpatient, <i>n</i> (%)	595 (38.9)	323 (31.4)	272 (54.2)	73.7 <sup>†</sup>	1	<0.001
Health insurance coverage, <i>n</i> (%)	1129 (73.7)	763 (74.1)	366 (72.9)	0.2 <sup>†</sup>	1	0.600
Family history of psychiatric disorders, <i>n</i> (%)	212 (13.8)	129 (12.5)	83 (16.5)	4.5 <sup>†</sup>	1	0.300
Delusions or hallucinations in the past month, <i>n</i> (%)	42 (2.7)	2 (0.2)	40 (8.0)	76.4 <sup>†</sup>	1	<0.001
Suicidality in the past month, <i>n</i> (%)	340 (22.2)	213 (20.7)	127 (25.3)	4.1 <sup>†</sup>	1	0.040
Hospital level, <i>n</i> (%)						
Level-II	645 (42.1)	457 (44.4)	188 (37.5)	6.7 <sup>†</sup>	1	0.010
Level-III	886 (57.9)	572 (55.6)	314 (62.5)			
Age (years, mean ± SD)	44.0 ± 14.9	44.1 ± 14.8	43.7 ± 15.2	0.4 <sup>‡</sup>	1529	0.660
Age of onset (years, mean ± SD)	39.3 ± 14.5	39.8 ± 14.4	38.2 ± 14.6	1.9 <sup>‡</sup>	1529	0.048
Duration of illness (years, mean ± SD)	4.8 ± 6.5	4.5 ± 6.1	5.5 ± 7.2	-2.6 <sup>‡</sup>	—*	0.009
CGI-S (mean ± SD)	3.4 ± 1.3	3.4 ± 1.3	3.6 ± 1.3	-2.7 <sup>‡</sup>	1529	0.006
TESS total (mean ± SD)	0.9 ± 1.4	0.8 ± 1.2	1.1 ± 1.7	-2.4 <sup>‡</sup>	—*	0.010
Patients' satisfaction (mean ± SD)	5.0 ± 0.9	5.1 ± 0.9	4.9 ± 0.9	-4.5 <sup>‡</sup>	—*	<0.001
Families' satisfaction (mean ± SD)	5.1 ± 0.9	5.2 ± 0.9	5.0 ± 0.8	-4.1 <sup>‡</sup>	—*	<0.001
SF-12 physical (mean ± SD)	46.4 ± 8.8	46.4 ± 8.8	46.4 ± 8.8	0.04 <sup>‡</sup>	1529	0.960
SF-12 mental (mean ± SD)	32.5 ± 12.2	33.2 ± 12.4	30.8 ± 11.5	3.6 <sup>‡</sup>	1529	<0.001

\*Mann-Whitney *U*-test; <sup>†</sup>Chi-square values; <sup>‡</sup>*t* values in independent-samples *t*-test or *Z* value in Mann-Whitney *U*-test. CGI-S: Clinical Global Impressions-Severity scale; SF-12: Medical Outcomes Study Short Form 12; TESS: Treatment Emergent Symptom Scale; SD: Standard deviation.



**Table 4: The five most commonly prescribed antipsychotic drugs for MDD in China in year 2002, 2006, and 2012 (n (%))**

2002 (n = 126)		2006 (n = 282)		2012 (n = 502)	
Sulpiride	57 (45.2)	Olanzapine	66 (23.4)	Olanzapine	204 (40.6)
Perphenazine	20 (15.9)	Risperidone	50 (17.7)	Quetiapine	162 (32.3)
Risperidone	17 (13.5)	Quetiapine	47 (16.7)	Risperidone	58 (11.6)
Clozapine	11 (8.7)	Sulpiride	38 (13.5)	Sulpiride	24 (4.8)
Olanzapine	10 (7.9)	Perphenazine	33 (11.7)	Aripiprazole	19 (3.8)

Percentage of all patients on antipsychotic medications. MDD: Major depressive disorder.

adjunctive olanzapine, risperidone, quetiapine, and aripiprazole in the treatment of MDD.<sup>[4]</sup> The American Psychiatric Association guideline also does not differentiate between individual SGAs in its recommendations as add-on drugs for MDD.<sup>[18]</sup>

In this study, concurrent antipsychotic use in MDD was associated with a number of clinical variables. Antipsychotics have been recommended mainly to be used in treatment-refractory MDD.<sup>[4]</sup> This recommendation could explain the association of antipsychotic use with inpatient treatment, Level-III hospitals and longer duration of illness because these factors are more likely to be linked with treatment-resistance. The Chinese Medical Association<sup>[19]</sup> recommended the concurrent use of antipsychotics in treating MDD with psychotic symptoms, which probably explains the association between antipsychotic prescriptions and delusions or hallucinations. As expected, concurrent use of antipsychotics was associated with more side effects as measured by the TESS.

Multivariate analyses revealed that compared to the nonantipsychotic group, MDD patients on antipsychotics was associated with poorer patients' and families' satisfaction with treatment. This may be attributed to more frequent adverse effects, higher cost of treatment, and reduced treatment adherence associated with antipsychotics.<sup>[20-22]</sup> This association between severity of illness and dissatisfaction with the efficacy of the treatment could not be excluded. Surprisingly, however, there was no association between QOL and antipsychotic use, which could be partly attributed to the uncontrolled patients' and their families' economic level. This striking finding needs to be replicated in future studies.

There are several limitations to this study. First, due to its cross-sectional design, the causal relationship between concurrent antipsychotic use and other variables could not be examined. Second, the reasons for prescribing antipsychotics were not identified. There are differences in prescribing practices and treatment guidelines between institutions even within one province or municipality. Finally, the diagnosis of depression was established by a review of medical records and a clinical interview, rather than using a structured diagnostic interview schedule. These limitations are partly offset by the study's strengths including its large, homogeneous, and representative sample.

In conclusion, about one in four depressed patients received antipsychotic medication in this study, which

has increased over time. Considering the increased risk of antipsychotic-induced side effects and patients' and their families' lack of satisfaction with psychiatric treatment in general, further examination of the rationale and appropriateness of antipsychotic prescription for depression and its alternatives is warranted.

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