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Adjunctive antidepressant use in schizophrenia in China: a national survey (2002-2012)

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Abstract

Objective: This study examined the pattern of adjunctive antidepressant use in schizophrenia patients, and its demographic and clinical correlates in a nationwide survey in China.

Methods: A total of 14,013 patients in 45 Chinese psychiatric hospitals/centers were interviewed (4,486 in 2002, 5,288 in 2006 and 4,239 in 2012). Patients' socio-demographic and clinical characteristics were recorded using a standardized protocol and data collection procedure. Chi-square test, independent-samples t-test, Mann–Whitney U test and multiple logistic regression analysis were used in data analyses.

Results: Antidepressant use was found in 5.2% of the study population with 4.6% in 2002, 4.3% in 2006 and 6.9% in 2012, respectively. A significant increase in use from 2006 to 2012 was found ($p < 0.001$). Multiple logistic regression analyses in the whole population revealed that patients receiving adjunctive antidepressants were more likely to be outpatients in tertiary referral centers (Level-III hospitals) and who had an earlier age of onset, less severe global illness but more depressive symptoms. They were less likely to receive first-generation antipsychotics, but more likely to receive benzodiazepines ($R^2 = 0.255$, $p < 0.001$).

Conclusions: Despite an increasing trend, the frequency of antidepressant use in schizophrenia in China was considerably lower than in Western countries. The benefits and risks associated with concomitant use of antidepressants in schizophrenia need to be studied further.

Key words: Schizophrenia, Antidepressants, China

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INTRODUCTION

Co-existing depressive symptoms are common at all stages of schizophrenia. They occur in up to 70% of schizophrenia patients (Buckley *et al.*, 2009; Romm *et al.*, 2010), which can result in potentially serious consequences, such as high risk for suicide, frequent relapse and poor quality of life (Evensen *et al.*, 2012; Mauri *et al.*, 2013). As the mainstay treatment for clinical depression, antidepressants have often been prescribed in schizophrenia, although convincing evidence of benefits in clinical practice is still lacking (Himmelhoch *et al.*, 2012). In addition, antidepressants are often prescribed for comorbid obsessive-compulsive disorder or anxiety disorder, and sometimes even for cognitive deficits and negative symptoms (Cho *et al.*, 2011; Silver, 2003).

In order to justify its use, it is important to understand the pattern of antidepressant use in clinical practice. Current literature showed that 17%-64% of schizophrenia patients received antidepressants (Kiviniemi *et al.*, 2013; Mundt *et al.*, 2012; Vares *et al.*, 2011). However, most studies are done in Western countries, while very limited data are from China. Only a few regional surveys of adjunctive antidepressants in Chinese schizophrenia patients have been done. For example, An *et al.* (An *et al.*, 2010) reported that the percentage of adjunctive antidepressant use in schizophrenia was 4.3% in 1999 and 9.5% in 2008 in a psychiatric hospital in Beijing. In a large-scale

pharmaco-epidemiological project entitled the Research on Asian Psychotropic Prescription Pattern (REAP) study involving six Asian countries and territories, 6.8% of schizophrenia patients in China received antidepressants (Xiang *et al.*, 2013). Since data from only four psychiatric hospitals were obtained, the findings are unlikely to reflect nationwide patterns.

This study set out to examine the use of adjunctive antidepressants in schizophrenia in a national survey of psychotropic prescription along with its demographic and clinical correlates.

METHOD

Study design and participants

This study was part of a national, iterative, cross-sectional pharmaco-epidemiological survey project conducted in China and initiated by the Chinese Society of Psychiatry. The initial survey was conducted in May 2002 and two follow-up surveys were done in May 2006 and July-August 2012 using the same design and a standardized protocol (Si *et al.*, 2004). Altogether 45 mental health hospitals/centers located in 10 provinces and municipalities including Beijing, Guangdong, Hebei, Hubei, Jiangxi, Jiangsu, Jilin, Shaanxi, Shanxi and Sichuan participated in each survey. Inpatients and outpatients treated in the participating hospitals/centers during the study period were consecutively

screened for eligibility. All members of the research team were trained psychiatrists. Inclusion criteria were: (1) DSM-IV or ICD-10 diagnosis of schizophrenia based on review of medical records and a clinical interview; (2) age 15 years or older; (3) on any antipsychotic drugs; (4) had the ability to understand the contents of the survey. The study protocol was approved by the Ethics Committees of the participating hospitals. All patients provided written informed consent.

Assessments and evaluation

Basic socio-demographic and clinical characteristics were collected using a data collection form designed for the study. Information about the types and doses of all psychotropic drugs were collected from medical records. Doses of antipsychotic drugs were converted into chlorpromazine equivalent milligrams (CPZeq) (APA, 1997; Woods, 2003). The cumulative doses of all antipsychotics prescribed at the time of the survey were used for analyses. Antipsychotic polypharmacy was defined as the concurrent prescription of 2 or more antipsychotics (Xiang *et al.*, 2012). Following the same procedures of the Research on Asian Psychotropic Prescription (REAP) project (Xiang *et al.*, 2012), positive and negative symptoms, depressive symptoms in the past month were evaluated and recorded during the diagnostic interview in all three surveys.

Global illness severity was evaluated with the Chinese versions of the Clinical Global Impressions-Severity scale (CGI-S) (Guy, 1976). The Treatment Emergent Symptom Scale (TESS) (National Institute of Mental Health, 1985) was used to record drug-induced side effects. 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 the best medical equipment, while Level-II hospitals are regional medical centers that treat patients with severe diseases, and level-I hospitals are small, community level hospitals, only providing basic medical care. There was no Level-I psychiatric hospital at the study time in the areas included, thus, only Level-III/II medical facilities were involved in this study. 'Adjunctive antidepressants' refer to the concurrent use of antidepressants in treating schizophrenia patients.

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, comparison between the antidepressant and non-antidepressants groups in terms of demographic and clinical variables were made using chi-square tests, independent-samples t-tests or Mann-Whitney U tests, 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 independently and significantly associated with the use of antidepressants. Antidepressant prescription was the dependent variable, while the variables that significantly differed between the two groups in univariate analyses were entered as independent variables. Statistical significance of all analyses was set at 0.05 (two-tailed).

RESULTS

A total of 14,013 patients were included in the analyses, comprising 4,486 in 2002, 5,288 in 2006 and 4,239 in 2012. In the combined sample of 2002-2012, 5.2% patients were co-prescribed antidepressants, with 4.6% in 2002, 4.3% in 2006 and 6.9% in 2012. There was no significant difference in the percentage of concomitant antidepressant prescriptions between 2002 and 2006 ($\chi^2=0.675$, $df =1$, $p= 0.220$), but a significant increase was found between 2006 and 2012 ($\chi^2=20.5$, $df =1$, $p<0.001$).

Table 1 shows the socio-demographic and clinical characteristics of the pooled sample and separately for the antidepressant and non-antidepressant groups. Table 2 presents the variables that are independently and significantly associated with antidepressants. Patients on antidepressants were more likely to be treated as outpatients in Level-III hospitals, and who had an earlier age of

onset, less severe global illness, but more severe depressive symptoms. They were more likely to receive benzodiazepines, but less likely to receive first-generation antipsychotics (FGAs). These variables together accounted for 25.5% of the variance of antidepressants utilization ($p < 0.001$). Table 3 shows the six most commonly co-prescribed antidepressants in the three surveys.

DISCUSSION

The increasing trend of antidepressant use observed in this study may be related to the widespread use of newer antidepressants and the growing impact of pharmaceutical companies on clinical practice. The figure in the pooled sample (5.2%) however was much lower than those reported in Western studies (Himmelhoch *et al.*, 2012), but similar to the rate (6.8%) found in the REAP study (Xiang *et al.*, 2013). The lower rate of antidepressants use in Chinese schizophrenia patients may be related to the lack of treatment guidelines in China to treat comorbid depression (Xiang *et al.*, 2013). The rationale for concomitant use of antidepressant in schizophrenia have been controversial. A Cochrane systematic review concluded that there was no convincing evidence to support or refute use of antidepressants for depression in schizophrenia (Whitehead *et al.*, 2002). In contrast, a recent meta-analysis found that augmentation with antidepressants was associated

with a low risk of exacerbation of psychosis and adverse effects (Helfer *et al.*, 2016).

Although not measured in this study, the frequent occurrence of anxiety and insomnia in co-morbid depression with schizophrenia could account for the positive association between antidepressant and benzodiazepine prescriptions. Schizophrenia patients with a younger age of onset are more prone to have complex clinical presentations, including comorbid depressive symptoms (Masi *et al.*, 2006), which may lead to increased use of antidepressants. Psychiatric stigma and discrimination attached to schizophrenia patients and their families is a major reason for post-psychotic depression in China (Lee *et al.*, 2005). Denial of illness by their family in an attempt to protect family reputation and avoid public shame and marginalization, can often lead to negative impact on mood (Misdrahi *et al.*, 2014). This may account for the increasing use of antidepressants in outpatients and those with less severe global illness.

In order to minimize treatment cost, FGAs are frequently considered for patients who lack health insurance. For similar reasons, polypharmacy, such as adjunctive antidepressants, are less likely to be prescribed for this population, which may partly explain the negative association between use of FGAs and antidepressants. Patients with comorbid depression are usually more likely to be referred to level-III tertiary hospitals,

which may explain the increased use of antidepressants in this setting.

There are several limitations in this study. First, due to its cross-sectional design, the causality between antidepressant use and other variables could not be examined. In addition, some variables such as age of onset and family history of psychiatric disorders, were collected retrospectively. Second, the psychotic and mood symptoms were only measured with a binary variable, whereas global illness severity was evaluated with the CGI-S. Third, patients were only recruited from Level-III/II medical facilities.

In conclusion, the frequency of antidepressant use in schizophrenia patients in China was considerably lower compared to their counterparts in Western settings. The benefits and risks associated with concomitant use of antidepressants in schizophrenia patients warrant further research.

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Table 1. Comparison between the antidepressants and non-antidepressants groups with respect to basic demographic and clinical variables (2002-2012)

	Total sample (n=14013)		Non-antidepressant (n=13286)		Antidepressant (n=727)		statistics		
	N	%	N	%	N	%	χ^2	df	p
Male sex	7414	52.9	7062	53.2	352	48.4	6.2	1	0.01
Inpatient status	7944	56.7	7592	57.1	352	48.4	21.4	1	<0.001
Having insurance	6667	47.6	6300	47.4	367	50.5	2.6	1	0.11
Family history of psychiatric disorders	3019	21.5	2864	21.6	155	21.3	0.02	1	0.88
Positive symptoms in the past month	9221	65.8	8785	66.1	436	60.0	11.6	1	0.001
Negative symptoms in the past month	6055	43.2	5715	43.0	340	46.8	4.0	1	0.047
Depressive symptoms in the past month	988	7.1	649	4.9	339	46.6	1832.9	1	<0.001
On FGAs	5619	40.1	5405	40.7	214	29.4	36.3	1	<0.001
On SGAs	10619	75.8	10021	75.4	598	82.3	17.5	1	<0.001
On APP	4052	28.9	3841	28.9	211	29.0	0.004	1	0.95
On benzodiazepines	2740	19.6	2565	19.3	175	24.1	10.0	1	0.002
Hospital level							52.3	1	<0.001
Level-III	5885	42.0	5486	41.3	399	54.9			
Level-II	8128	58.0	7800	58.7	328	45.1			
	Mean	SD	Mean	SD	Mean	SD	T / Z	df	p
Age (years)	35.6	13.1	35.7	13.1	33.8	12.6	3.8	14011	<0.001
Onset age (year)	27.3	10.4	27.4	10.4	25.6	10.2	4.6	14011	<0.001
Duration of illness (years)	8.3	9.3	8.3	9.3	8.2	9.2	-0.8	- ^a	0.44
CGI-S	3.9	1.5	4.0	1.5	3.7	1.4	3.9	14011	<0.001
TESS total 1	2.5	4.3	2.4	4.3	3.1	3.7	-6.3	- ^a	<0.001
CPZeq	414.7	309.3	413.8	306.0	429.9	364.5	-1.3	- ^a	0.20

a: Mann-Whitney U test; APP=Antipsychotic polypharmacy; CGI-S=Clinical Global Impressions-Severity scale; CPZeq=chlorpromazine equivalent milligrams; FGAs=first-generation antipsychotics; SGAs=second-generation antipsychotics; TESS=Treatment Emergent Symptom Scale; T/Z = t value in independent-samples t tests or z value in Mann-Whitney U test

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Table 2. Factors associated with antidepressant use in the pooled sample (n=14,013). Multiple logistic regression analysis with non-antidepressants group as the reference

	P value	Odds ratio	95% CI	
Age (year)	0.83	1.001	0.9	1.01
Male gender	0.36	0.9	0.7	1.09
Inpatient	0.001	0.7	0.6	0.8
Positive symptoms	0.12	0.8	0.7	1.04
Negative symptoms	0.10	1.1	0.9	1.3
Depressive symptoms	<0.001	20.4	17.0	24.5
On FGAs	0.001	0.6	0.4	0.8
On SGAs	0.38	0.8	0.6	1.1
On benzodiazepines	0.04	1.2	1.0002	1.4
Hospital level				
Level-II	---	1.0	---	---
Level-III	<0.001	1.8	1.5	2.1
Age of onset (years)	0.007	0.98	0.97	0.99
CGI-S	0.001	0.89	0.84	0.95
TESS total	0.2	1.01	0.99	1.02
Study time				
2002	---	1.0	---	---
2006	0.55	1.06	0.8	1.3
2012	<0.001	1.6	1.2	2.0

Total R²=0.255, P<0.001; the study sites have been controlled for; CGI-S=Clinical Global Impressions-Severity scale; FGAs=first-generation antipsychotics; GAs=second-generation antipsychotics; TESS=Treatment Emergent Symptom Scale

Table 3. Most common antidepressants used in Chinese schizophrenia patients

2002			2006			2012		
	n	%		n	%		n	%
cloimipramine	63	1.4	fluoxetine	72	1.4	sertraline	87	2.1
fluoxetine	47	1.0	venlafaxine	31	0.6	fluoxetine	58	1.4
doxepine	27	0.6	cloimipramine	29	0.5	paroxetine	37	0.9
venlafaxine	20	0.4	paroxetine	23	0.4	escitalopram	21	0.5
amitriptyline	19	0.4	sertraline	13	0.2	fluvoxamine	21	0.5
maprotiline	11	0.2	amitriptyline	10	0.2	cloimipramine	19	0.4

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