

Increased Use of Antidepressants in Wuhan, China: a Retrospective Study From 2006 to 2012

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Key Words: antidepressant; daily drug cost; defined daily dose; selective serotonin reuptake inhibitors; traditional Chinese patent medicines.

Summary. *Objective.* The aim of this study was to investigate the trend of antidepressant use and analyze the daily cost of antidepressants in Wuhan, China.

Material and Methods. The data on the expenditure of antidepressants in Wuhan from 2006 to 2012 were retrospectively analyzed based on the defined daily dose (DDD) method recommended by the World Health Organization. In addition, the daily cost of antidepressants was calculated for the pharmacoeconomic evaluation.

Results. The overall sales of antidepressants increased by 566.7% over the 7-year period. The utilization of antidepressants increased annually from 1.067 DDDs per 1000 inhabitants per day in 2006 to 4.144 in 2012. This upward trend was mainly driven by an increase in the use of selective serotonin reuptake inhibitors (SSRIs), which accounted for about 60% of antidepressant use. Notably, the use of traditional Chinese patent medicines (TCMs) approved to treat depression in China in 2010 increased from 0.158 DDDs per 1000 inhabitants per day in 2010 to 0.305 in 2012. The daily drug cost analysis indicated that selective serotonin and norepinephrine reuptake inhibitors (SNRIs) and other new antidepressants were more expensive while tricyclic and tetracyclic antidepressants (TCAs) had a low-cost advantage.

Conclusions. Antidepressants were increasingly used over the study period. Among them, SSRIs followed by SNRIs were the most commonly used. After the approval for the treatment of depression, TCMs were generally accepted by physicians and patients. The low-cost advantage allowed TCAs to be used in the antidepressant therapy.

Introduction

The Global Burden of Diseases Study 2010 has indicated that depression is the most disabling disease worldwide according to years lived with disability and is the fourth leading cause of the overall disease burden measured in disability-adjusted life years (1). In parallel with the growth in the prevalence of depression, antidepressant use is increasing dramatically over time. In the United States, the rate of antidepressant treatment increased from 5.84% in 1996 to 10.12% in 2005 (2). In 29 European countries, an average growth in the use of antidepressants during the last 5 years was 19.83% (3). Similarly, upward trends were also noted in other countries (4, 5). This increase may be attributed to the introduction of new antidepressants, including selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), and other new antidepressants.

Although several studies have documented an increased use of antidepressants in other countries, little is known regarding the use of antidepressants

in China from an international perspective as most studies have been published in Chinese (6). Despite having a lower incidence rate than the worldwide average, China has witnessed an explosive increase in the number of patients with depression, which may be due to aggravated aging and high susceptibility of the elderly (7). Furthermore, drug consumption is very high in China due to the large population; therefore, rational drug utilization in China is very important.

Thus, the aim of this study was to explore the trends of prevalence and pattern of antidepressant use in China. Wuhan, the capital of Hubei Province, is one of the 7 metropolises in China and the biggest city of central China, having 13 administrative areas and 10.02 million residents. The utilization patterns of antidepressants in 32 hospitals in Wuhan from 2006 to 2012 were retrospectively analyzed to assess the antidepressant prescription pattern and to provide evidence for safe, effective, and economized drug selection.

Material and Methods

Data Source. Information on drug utilization in 32 hospitals located in the different administrative districts of Wuhan, registered in the “Hospital

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Purchase of Drug Information System” from 2006 to 2012, was provided by the Scientific and Technical Information Institute of Shanghai Food and Municipal Drug Administration. There are 13 administrative districts in Wuhan including 7 urban districts and 6 rural districts. Twenty-one class III hospitals (the highest grade in the Chinese hospital classification system) mainly from urban districts as well as 9 class II and 2 class I hospitals mainly from rural districts were selected, thus rendering the results representative of the utilization of antidepressants in Wuhan.

Methods. By using common names as the units, the consumption and sales of antidepressants were summarized. The World Health Organization Anatomical Therapeutic Chemical (ATC) Classification system with defined daily doses (DDDs) was applied. The DDDs of drugs that were not included in the ATC Classification system were derived from the Chinese Pharmacopoeia (2010 Edition) and the Newly Compiled Pharmacology (16th Edition). The utilization of antidepressants was expressed in DDDs per 1000 inhabitants per day.

Drug utilization research has extensively been conducted to evaluate drug use in China, and a DDD as well as the daily drug cost (DDC) are popular concepts adopted in most drug utilization researches (8). Since patients with clinical depression require long-term treatment, it is important to take into account not only safety, tolerance, and therapeutic effects, but also costs of a drug (9). The DDC gives information about the average daily cost of a certain drug. The conception of DDC was originally proposed in China in a large-scale study by Zou et al. in 1996 (10). $DDC = \text{annual drug cost [US \$]} / (\text{annual consumption quantity [g]} / \text{DDD [g/d]})$. The daily treatment cost can be estimated according to the DDC, based on which drugs can be rationally selected while considering the economic burden and disease progression of a patient.

Results

Use of Antidepressants by Year. The use of antidepressants by different pharmacological classifications and every antidepressant are shown in Fig. 1 and Table 1, respectively. The utilization of antidepressants increased by 288.4% from 1.067 DDDs per 1000 inhabitants per day in 2006 to 4.144 DDDs per 1000 inhabitants per day in 2012. As shown in Fig. 1, except for a marginal increase in the use of SNRIs and other antidepressants, the dramatic changes in prescription can be mainly attributable to SSRIs. The use of SSRIs accounted for about 60% (56.3%–61.9%) of antidepressant use during the study period. Before 2010, the use of fluoxetine, venlafaxine, citalopram, paroxetine, and mirtazapine was the greatest, among which the values of citalopram and paroxetine rose significantly. The use

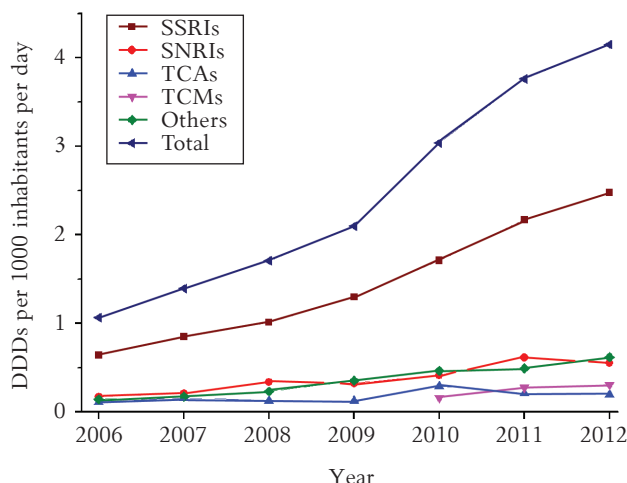


Fig. 1. Use of antidepressants in defined daily doses (DDDs) per 1000 inhabitants per day by different pharmacological classifications during 2006–2012

SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective serotonin and norepinephrine reuptake inhibitors; TCAs, tricyclic and tetracyclic antidepressants; TCMs, traditional Chinese patent medicines.

of escitalopram sharply increased from 0.042 DDDs per 1000 inhabitants per day in 2009 to 0.589 DDDs per 1000 inhabitants per day in 2012, and this drug has become one of the 5 best-selling drugs since 2010.

Notably, of the 9 new drugs introduced in 2010, 4 were prepared from traditional Chinese medicines (TCMs). The use of TCMs was increasing annually with DDDs per 1000 inhabitants per day being 0.158 in 2010 and 0.305 in 2012. The use of Shugan Jieyu capsules contributed mainly to this increase as their use increased by 167.5%. As for other drugs, the use of trazodone and duloxetine rose significantly. On the contrary, the utilization of tricyclic or tetracyclic antidepressants (TCAs) was low and accounted only for 3.4% of all the prescriptions in 2012, although there was a transient growth in 2010.

Sales of Antidepressants by Year. The sales of antidepressants of different pharmacological classifications are displayed in Fig. 2. The overall sales of antidepressants in Wuhan was steadily increasing, and it increased by 566.7% from \$1.2 million in 2006 to \$6.8 million in 2012, with the highest growth rate of 64.1% in 2009 and the lowest growth rate of 11.2% in 2012. Other kinds of antidepressants, except TCAs, showed an upward tendency. Fluoxetine, venlafaxine, citalopram, paroxetine, and mirtazapine ranked the top 5 during 2006–2009, reaching more than 80% market share. The sales of escitalopram increased sharply and ranked first in 2012. In contrast, expenditure on TCAs remained stable during the 7 year-period despite a peak of \$0.05 million in 2010.

Table 1. Use of Antidepressants in Defined Daily Doses per 1000 Inhabitants per Day During 2006–2012

Antidepressant	2006	2007	2008	2009	2010	2011	2012
Selective serotonin reuptake inhibitors							
Fluoxetine	0.260	0.271	0.237	0.312	0.294	0.384	0.313
Citalopram	0.153	0.284	0.357	0.383	0.559	0.713	0.461
Paroxetine	0.141	0.194	0.258	0.362	0.464	0.489	0.639
Fluvoxamine	0.062	0.058	0.080	0.114	0.117	0.075	0.145
Sertraline	0.029	0.044	0.078	0.085	0.126	0.210	0.330
Escitalopram	NA	NA	0.000	0.042	0.149	0.299	0.589
Selective serotonin and norepinephrine reuptake inhibitors							
Venlafaxine	0.171	0.207	0.292	0.266	0.311	0.481	0.371
Duloxetine	NA	0.003	0.045	0.057	0.102	0.134	0.181
Tricyclic or tetracyclic antidepressants							
Doxepin	0.051	0.049	0.043	0.030	0.151	0.059	0.059
Amitriptyline	0.031	0.065	0.054	0.051	0.054	0.104	0.105
Clomipramine	0.028	0.045	0.030	0.043	0.086	0.047	0.029
Manserine	NA	NA	NA	NA	0.001	0.001	0.003
Traditional Chinese medicine antidepressants							
Jieyu pills	NA	NA	NA	NA	0.068	0.068	0.057
St. John's Wort	NA	NA	NA	NA	0.063	0.114	0.067
Shugan Jieyu capsules	NA	NA	NA	NA	0.027	0.091	0.180
Jiuwei Zhenxin granules	NA	NA	NA	NA	NA	NA	0.001
Other antidepressants							
Mitrazapine	0.105	0.119	0.133	0.169	0.179	0.173	0.314
Tianeptine	0.026	0.013	0.008	0.008	0.004	NA	NA
Trazodone	0.012	0.043	0.091	0.142	0.243	0.282	0.279
Reboxetine	NA	NA	NA	0.033	0.024	0.019	0.012
Amfebutamone	NA	NA	NA	NA	0.013	0.016	0.009
Total	1.067	1.393	1.706	2.098	3.035	3.759	4.144

NA, not available.

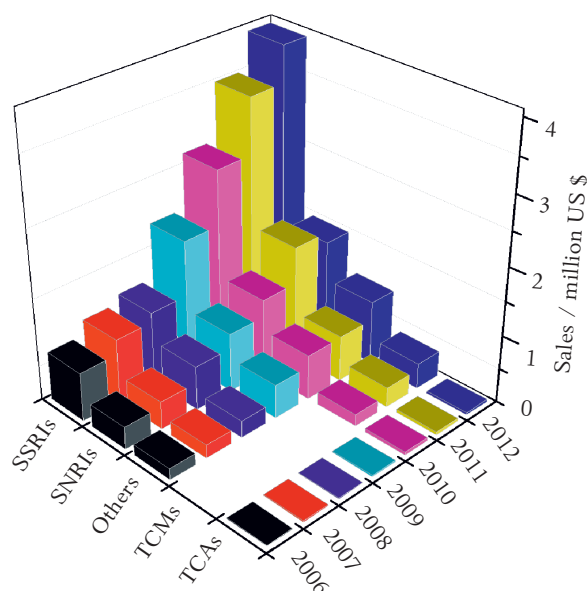


Fig. 2. Sales of antidepressants by different pharmacological classifications during 2006–2012

SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective serotonin and norepinephrine reuptake inhibitors; TCAs, tricyclic and tetracyclic antidepressants.

DDC of Antidepressants. As shown in Table 2, the average DDC of SNRIs and other new antidepressants was relative higher as compared with that of TCAs. The DDC of 11 drugs decreased within the 7-year period, and that of the other drugs fluctuated little and hardly rose. The DDC of Jiuwei Zhenxin granules, duloxetine, venlafaxine, and escitalopram, which were introduced in China later, was the highest. Contrarily, the DDC of the majority of TCAs, such as doxepin, amitriptyline, and clomipramine, as well as St. John's Wort was the lowest.

Discussion

To our knowledge, this is the first study to collect and report information about antidepressant consumption in China over a 7-year period. Two major trends were observed in our study. First, the utilization of antidepressants kept increasing during 7 years, which was mainly attributed to the increased use of SSRIs. Second, TCMs were approved to treat depression in China and were generally accepted by physicians and patients.

The utilization of antidepressants increased by 2.9 fold during the study period, which may be attributed to the improved tolerance of new antidepressants, thus treatment persistence was enhanced.

Table 2. The Daily Drug Cost (US \$/day) of Antidepressants During 2006–2012

Antidepressant	2006	2007	2008	2009	2010	2011	2012	Average
Selective serotonin reuptake inhibitors								1.71
Fluvoxamine	1.13	1.13	1.13	1.12	1.14	1.12	1.11	1.13
Citalopram	1.70	1.62	1.39	1.22	1.14	1.24	1.09	1.34
Fluoxetine	1.55	1.51	1.48	1.51	1.51	1.47	1.43	1.49
Paroxetine	1.70	1.67	1.66	1.55	1.56	1.54	1.55	1.60
Sertraline	2.29	2.17	2.17	2.17	2.10	2.02	2.01	2.13
Escitalopram	NA	NA	2.62	2.60	2.60	2.56	2.41	2.56
Selective serotonin and norepinephrine reuptake inhibitors								2.78
Venlafaxine	2.79	2.81	2.75	2.70	2.51	2.60	2.59	2.68
Duloxetine	NA	2.89	2.89	2.89	2.91	2.89	2.89	2.89
Tricyclic or tetracyclic antidepressants								0.65
Doxepin	0.07	0.07	0.07	0.06	0.06	0.07	0.07	0.07
Amitriptyline	0.11	0.11	0.10	0.11	0.12	0.11	0.11	0.11
Clomipramine	0.42	0.37	0.37	0.25	0.37	0.47	0.42	0.38
Mianserine	NA	NA	NA	NA	2.07	2.05	2.05	2.05
Traditional Chinese medicine antidepressants								1.82
St. John's Wort	NA	NA	NA	NA	0.55	0.55	0.55	0.55
Shugan Jieyu capsules	NA	NA	NA	NA	1.37	1.37	1.37	1.37
Jieyu pills	NA	NA	NA	NA	1.48	1.48	1.48	1.48
Jiuwei Zhenxin granules	NA	NA	NA	NA	NA	NA	3.87	3.87
Other antidepressants								1.42
Tianeptine	0.77	0.76	0.76	0.76	0.76	NA	NA	0.76
Trazodone	1.14	0.99	0.98	0.98	0.98	0.98	0.98	1.01
Reboxetine	NA	NA	NA	1.15	1.15	1.16	1.15	1.15
Mirtazapine	1.96	1.96	1.98	1.85	1.78	1.76	1.84	1.88
Amfebutamone	NA	NA	NA	NA	2.31	2.31	2.31	2.31

NA, not available.

Nevertheless, the value of DDDs per 1000 inhabitants per day was still lower than that of many countries (3). In fact, the prevalence of major depressive disorder in Wuhan reached 9.4% in 2009 (11), far more than the utilization of antidepressants. This disparity indicated that depression was undertreated in Wuhan, which is common in China. An earlier study in 4 provinces of China suggested that of the 173 million adults with a mental disorder, 158 million have never received any type of professional help for their condition, and the reasons for this phenomenon was also discussed in that study (12).

This study showed that SSRIs were the most commonly prescribed antidepressants during the 7-year period, which may be due to their fewer adverse reactions, easier dosing, and lower number of overdose deaths. Some similar research conducted in other countries has also shown the advantage of SSRIs (13, 14). Escitalopram, a new SSRI, was rapidly popularized in Wuhan immediately after it was approved for clinical use in 2008. Its popularity can be explained by good acceptability and superb therapeutic effects (15). In this study, the DDC of escitalopram ranked fourth among antidepressants, but the high daily cost did not lessen the enthusiasm of patients. A cost and quality-of-life pharmaco-economic analysis has also suggested that escitalopram, despite its tremendous cost, is preferred to other

antidepressants as the most cost-effective pharmacological treatment strategy (9).

The side effects and poor tolerance of chemical antidepressants encourage treatment with phytochemicals. After being introduced in Wuhan in 2010, St. John's Wort, Jieyu pills (pharmaceutical ingredients: *Bupleurum chinense* and *Paeonia sterniana*) and Shugan Jieyu capsules (pharmaceutical ingredients: St. John's Wort and *Eleutherococcus senticosus*) have exhibited a striking performance, with the DDDs per 1000 inhabitants per day of Shugan Jieyu capsules rising remarkably. In 2012, another TCM-based antidepressant, Jiuwei Zhenxin granules, composed of 9 Chinese herbal components also became available.

St. John's Wort, also known as *Hypericum perforatum*, is a well-known natural medicinal plant worldwide to treat clinical depression. It has been demonstrated that St. John's Wort mainly functions by binding to more than 30 types of receptors and reuptake transporters in the human body. This multitarget mechanism of action and consequently far fewer adverse reactions made St. John's Wort surpass chemical antidepressants (16). Many drugs based on medicinal plants such as *Acorus gramineus* (17), *Centella asiatica* (18), *Morinda officinalis* (19), *Eleutherococcus senticosus* (20), *Panax ginseng* (21), and *Paeonia sterniana* (22), etc. have been found to

be effective. TCMs treat clinical depression by multiple pharmacological ingredients acting via various pathways and targets. Meanwhile, a low dose of each ingredient frees patients from insufferable side effects, which are often caused by a large dose of chemical antidepressants. However, the complicated composition is a double-edged sword, which still lacks international credits for the difficulty in identification.

With venlafaxine and duloxetine as the eminent representatives, SNRIs are feasible in treating the patients whose depressive symptoms do not improve after 8 weeks' administration of SSRIs. Benefiting from their fast action, extensive indications, and a high DDC, the sales of venlafaxine ranked first from 2006 to 2011. Duloxetine has extensively been used since its introduction in Wuhan in 2007, which may be ascribed to its ability to effectively treat emotional and somatic symptoms as well as pain-related symptoms caused by prevailing antidepressants (23). Yet, the high daily cost may hinder the use of SNRIs in patients with low income.

As for other antidepressants, trazodone, with high safety and increased indications, was increasingly accepted in Wuhan. Trazodone at low doses (25–100 mg/d), as suggested by the Guidelines for the Diagnosis and Treatment of Adult Insomnia in China (2012 edition), can tranquilize the patients who stop using hypnotic drugs. On the other hand, sexual dysfunction, a common (25.8%–80.3%) side effect of second-generation antidepressants such as sertraline, venlafaxine, citalopram, paroxetine, and fluoxetine (24), is rare among the patients taking trazodone (25).

The DDC analysis indicated that TCAs were drugs of choice to minimize costs. However, the issues about their safety and tolerance made their utilization restricted. Of all the antidepressants, the use of monoamine oxidase inhibitors has been discontinued in Wuhan because of their severe adverse reactions.

Several limitations of this study should be considered. One limitation is that patient-specific information accompanying the utilization and cost data was absent. Therefore, we could not identify for which indications antidepressants are being used. Another limitation is the inherent shortcoming of the DDD methodology as it is only applicable to adults. In fact, the non-adult population accounts only for a minimal proportion of antidepressant users, so the impact of lack of information about age distribution is minimized.

Conclusions

Remarkably increased use and sales of antidepressants have been observed in Wuhan from 2006 to 2012. This continuous increase is mainly attributed to the increased use of SSRIs. Traditional Chinese patent medicines, which were approved to treat depression in 2010, are booming up. The other novel antidepressants such as duloxetine and trazodone are also commercially and clinically promising. Older antidepressants like TCAs were drugs of choice to minimize costs, but their use was restricted by their adverse effects.

Statement of Conflict of Interest

The authors state no conflict of interest.

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