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ORIGINAL RESEARCH

Trends in Combinatorial Endocrine Therapy for Breast Cancer Across Six Cities in China(2016-2021)

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Objective: This study aims to assess the prescribing patterns and combinations of endocrine therapy medications for breast cancer across six cities in China over a six-year period.

Methods: Data on outpatient prescriptions were sourced from the China Hospital Prescription Analysis Cooperative Project database. The study analyzed trends in endocrine therapy medications, focusing on the number of prescriptions, total costs, defined daily doses (DDDs), and defined daily costs (DDC). The study also examined the use of two-drug combinations separately for premenopausal and postmenopausal women.

Results: The number of prescriptions increased by 49.6% from 55,339 in 2016 to 82,791 in 2021. During the same period, annual costs ranged from 47.71 million to 88.37 million Chinese Yuan (CNY), marking an 85.2% increase. Tamoxifen, which led in DDDs in 2016, fell to sixth place, while exemestane rose from fifth to first place. Anastrozole's rank dropped from first to fourth, with letrozole consistently holding the second position in DDDs. Fulvestrant and goserelin consistently ranked among the top two in DDC. Conversely, toremifene and tamoxifen consistently occupied the lowest two positions in DDC. The combination of aromatase inhibitors (AI) and ovarian function suppression (OFS) represented the largest proportion among drug combinations, with its usage significantly increasing over the years ($P = 0.015$).

Conclusion: The use of endocrine therapy drugs has increased, with AI being the most frequently used. Additionally, the combination of AI and OFS has become the most prevalent treatment approach.

Keywords: breast cancer, endocrine therapy drugs, aromatase inhibitor, ovarian function suppression, combinatorial drug therapy

Introduction

As of 2020, breast cancer has overtaken lung cancer as the most commonly diagnosed cancer globally and ranks fifth in mortality. Among women, breast cancer is the leading cause of both incidence and mortality.[1] Treatment for breast cancer typically involves one or more of the following methods, either simultaneously or sequentially: surgery, chemotherapy, radiation therapy, endocrine therapy, targeted therapy, and immunotherapy.[2,3] Based on gene expression profiles, breast cancers are classified into three intrinsic subtypes: hormone-receptor positive (estrogen receptor (ER) or progesterone receptor), human epidermal growth factor receptor 2 (HER2) positive, and triple-negative breast cancer (TNBC).[4] ER positive breast cancer represents approximately 70% of all breast cancer cases.[5] For patients with ER-positive invasive breast cancer, adjuvant endocrine therapy is expected to provide clinical benefits across all stages.[6] However, given the wide array of medication choices available, it is necessary to conduct a statistical analysis of prescriptions in order to generate some recommendations.

The primary drug categories for endocrine therapy include selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs).[7] Additionally, ovarian function suppression (OFS), selective estrogen receptor down-regulators (SERDs),[8] and progesterone-based therapies are used. SERMs include tamoxifen and toremifene; AIs encompass anastrozole, letrozole, and exemestane; OFS consist of goserelin and leuprorelin; SERDs include fulvestrant; and progestogens feature megestrol. For premenopausal patients with ER-positive breast cancer, tamoxifen is the preferred treatment. A five-year course of tamoxifen reduces recurrence and mortality risks.[9] Postmenopausal patients are advised to use AI as adjuvant endocrine therapy for a duration of five years.[10] In premenopausal women at high risk of recurrence, combining ovarian function suppression with tamoxifen or exemestane offers greater benefits than

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tamoxifen alone.[11] Ovarian function suppression is particularly valuable for young patients wishing to preserve fertility.[12] An Italian study found that 85.9% of breast cancer patients received monotherapy, predominantly AI, with the most common combination being tamoxifen and ovarian function suppression.[13] A real-world study in China involving 1,877 patients with hormone receptor-positive HER2-negative metastatic breast cancer revealed a gradual increase in the use of endocrine therapy from 1996 to 2018, with 69% of patients using AI.[14]

Currently, for breast cancer patients with ER positive, endocrine therapy medications have better clinical benefits. However, in China, there is a paucity of large-scale, multi-city, retrospective analyses of prescriptions for breast cancer patients. The prescription patterns, treatment costs, and particularly the trends in combination drug therapies, remain poorly defined. Therefore, elucidating the current landscape of endocrine therapy medications for breast cancer is of paramount importance. This study analyzes outpatient prescription data from third-grade class-A hospitals across six Chinese cities from 2016 to 2021, with a total of approximately 430,000 prescriptions, aiming to elucidate the usage patterns and combinations of endocrine therapy medications and to provide a basis for improved anti-breast cancer medication management.

Methods

Data Source

Data on outpatient prescriptions for breast cancer were obtained from the Hospital Prescription Cooperation Project database.[15,16] The database included prescription data from 40 randomly selected sampling days annually, with 10 sampling days in each quarter, collected from the participating hospitals. Each prescription included details such as the prescription code, hospital code, prescription date, clinical department, patient's gender, age and diagnosis, and comprehensive information about the dispensed drug, including its name, size, dose, frequency, route of administration, and cost. The study was approved by the ethics committee of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University (20252025–01).

Study Population and Date Analysis

The screening and classification of prescription data were conducted using Microsoft Access. The study focused on prescriptions from female breast cancer patients aged 18–80 years, sourced from third-grade class-A hospitals across six cities: Beijing, Chengdu, Guangzhou, Hangzhou, Shanghai, and Harbin. The categorized prescription data were calculated and analyzed using Microsoft Office Excel® 2021.Defined Daily Doses (DDDs) were calculated by dividing the total annual dosage (in grams) by the DDD value (in grams), with DDD values derived from the World Health Organization's "ATC & DDD Index 2024". A higher DDDs value indicates a greater frequency of clinical use for the drug. Defined Daily Costs (DDC) were determined by dividing the total cost of each drug by its DDDs, reflecting the average daily medication cost. A higher DDC value signifies a greater economic burden on patients. The significance test for the correlation between the annual total number of prescriptions, total amount, DDDs, DDC and the year was performed using the Kendall tau-b method in SPSS software, with a confidence interval of 95%. Trend figures for DDDs and DDCs were generated using GraphPad Prism. The significance test for the correlation between the change in the proportion of combined drug use and the year was performed using the Kendall tau-b method in SPSS software, with a confidence interval of 95%. The specific analysis of whether there were significant differences in pairwise comparisons between years was conducted using two-way ANOVA in GraphPad Prism, and the results were visualized through graphical representation.

Results

Total Number, Cost, DDDs, and DDC of Endocrine Therapy Medications for Breast Cancer in Six Chinese Cities (2016-2021)

As indicated in Table 1, the total number of prescriptions for endocrine drugs used in breast cancer treatment generally increased, with a slight decline over the last two years. From 2016 to 2021, prescriptions rose from 55,339 to 82,791, reflecting a 49.6% increase. AI consistently had the highest number of prescriptions each year. Specifically, anastrozole was the most prescribed drug for the first five years but fell to third place in 2021. Letrozole consistently held second place, while exemestane surged from fifth place in 2016 to first place in 2021, indicating its growing clinical use and the changes were statistically significant ($P < 0.05$). Tamoxifen's prescription numbers remained relatively stable over the six

Table 1 Prescription Volume and Total Prescription Costs of Endocrine Therapy Medications for Breast Cancer Across Six Cities in China (2016–2021)

		Anastrozole	Letrozole	Exemestane	Toremifene	Tamoxifen	Fulvestrant	Goserelin	Leuprorelin	Megestrol	Total
2016	Pre num(n)	13,113	13,047	7,517	7,616	8,876	64	4,080	833	193	55,339
	Cost sum(¥)	12,259,295	11,982,162	9,560,597	2,360,300	378,647	698,996	8,275,783	2,140,041	53,868	47,709,689
2017	Pre num(n)	15,391	14,621	8,059	9,025	9,303	206	4,757	1,089	191	62,642
	Cost sum(¥)	13,735,065	12,599,037	9,991,558	2,767,720	398,128	1,668,257	9,236,195	2,691,216	48,871	53,136,047
2018	Pre num(n)	19,664	18,965	8,543	12,055	9,267	985	6,565	1,296	211	77,551
	Cost sum(¥)	16,574,135	15,245,722	9,994,017	3,338,320	378,082	4,713,120	12,121,420	3,607,168	44,582	66,016,566
2019	Pre num(n)	20,752	19,850	11,133	13,384	8,166	1,591	7,726	1,870	249	84,721
	Cost sum(¥)	17,252,255	14,539,908	11,500,570	3,579,179	528,798	7,402,260	14,054,817	5,149,233	52,595	74,059,617
2020	Pre num(n)	18,239	15,460	10,745	11,477	6,448	1,404	7,882	3,449	250	75,354
	Cost sum(¥)	21,528,961	16,550,377	15,805,209	4,282,345	1,027,988	6,888,022	18,868,260	8,539,744	53,450	93,544,355
2021	Pre num(n)	13,399	13,648	18,448	13,049	7,682	1,835	9,188	5,204	338	82,791
	Cost sum(¥)	6,782,376	6,807,821	28,308,888	5,327,234	1,498,613	8,779,264	17,262,708	13,530,602	73,812	88,371,318
	P_1	0.573	0.573	0.015	0.091	0.091	0.015	<0.01	<0.01	0.015	0.091
	P_2	0.348	0.573	<0.01	<0.01	0.039	0.015	0.015	<0.01	0.348	0.015

Notes: P_1, P value for the trend in the number of prescriptions; P_2, P value for the trend in the total costs. P_1 and P_2 were assessed by the Kendall tau-b trend test.

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Table 2 Distribution of DDDs (%) of Endocrine Therapy Medications for Breast Cancer Across Six Cities in China (2016–2021)

Drugs	2016	2017	2018	2019	2020	2021	P_1	P_2
Anastrozole	348261 (19.42)	430,687 (20.63)	556,761 (21.55)	616,633 (21.26)	808,480 (21.73)	643,746 (14.10)	0.015	0.573
Letrozole	367818 (20.51)	418,401 (20.04)	551,487 (21.34)	582,741 (20.09)	696,469 (18.72)	761,030 (16.67)	<0.01	0.091
Exemestane	226443 (12.63)	245,862 (11.77)	268,306 (10.38)	346,521 (11.95)	480,055 (12.90)	852,841 (18.68)	<0.01	0.188
Toremifene	265730 (14.82)	327,261 (15.67)	421,635 (16.32)	465,551 (16.05)	556,950 (14.97)	707,289 (15.49)	<0.01	0.851
Tamoxifen	376589 (21.00)	396,234 (18.98)	365,840 (14.16)	308,181 (10.62)	357,558 (9.61)	446,940 (9.79)	0.085	0.015
Fulvestrant	3660 (0.20)	12,810 (0.61)	59,760 (2.31)	96,300 (3.32)	89,610 (2.41)	115,290 (2.52)	0.015	0.039
Goserelin	121045 (6.75)	144,600 (6.93)	200,168 (7.75)	243,287 (8.39)	327,683 (8.81)	395,865 (8.67)	<0.01	0.015
Leuprorelin	78313 (4.37)	106,938 (5.12)	154,625 (5.98)	235,375 (8.11)	397,563 (10.69)	635,250 (13.91)	<0.01	<0.01
Megestrol	5091 (0.28)	5219 (0.25)	5230 (0.20)	6060 (0.21)	5855 (0.16)	8172 (0.18)	0.015	0.039
Total	1,792,950	2,088,011	2,583,812	2,900,650	3,720,222	4,566,423	<0.01	—

Notes: P_1, P value for the trend in the DDDs; P_2, P value for the trend in proportion of the DDDs; P_1 and P_2 were assessed by the Kendall tau-b trend test.

years. Toremifene showed a slight increase and remained stable overall. The prescriptions for Fulvestrant, Goserelin, Leuprorelin, and Megestrol have increased year by year ($P < 0.05$).

Overall, the total cost of the nine drugs increased year by year, but decreased in the final year, 2021. The trends in prescription costs and the number of prescriptions were largely consistent for the majority of the drugs. However, there were also certain changes that merit attention. According to Table 1, the prescription costs for anastrozole and letrozole experienced a marked decline in the final year of observation, specifically in 2021. Conversely, the cost of exemestane, another AI, rose significantly in 2021, likely due to an increase in prescription numbers. Tamoxifen and toremifene had lower total prescription costs due to their lower unit prices. Goserelin and leuprorelin, both ovarian function suppression, ranked high in total cost because of their higher unit prices. In general, the prescription costs for exemestane, toremifene, tamoxifen, fulvestrant, goserelin, and leuprorelin increased over the years ($P < 0.05$).

DDDs reflect drug usage frequency and clinical preference. As shown in Table 2, the DDDs of other drugs all increased with the years ($P < 0.05$), except for tamoxifen. Specifically, AI saw increased use, with exemestane ranking first in DDDs in 2021 and letrozole consistently holding second place. Toremifene remained stable in the third position, likely due to its effective therapy and lower price. Tamoxifen dropped from first place in 2016 to sixth place in 2020. Fulvestrant and megestrol consistently had low DDDs. Leuprorelin and exemestane showed the most rapid growth (as detailed in Figure 1). Anastrozole maintained the highest DDDs for four consecutive years but dropped to fourth place in 2021, reflecting the substantial decline in both prescription numbers and costs previously noted.

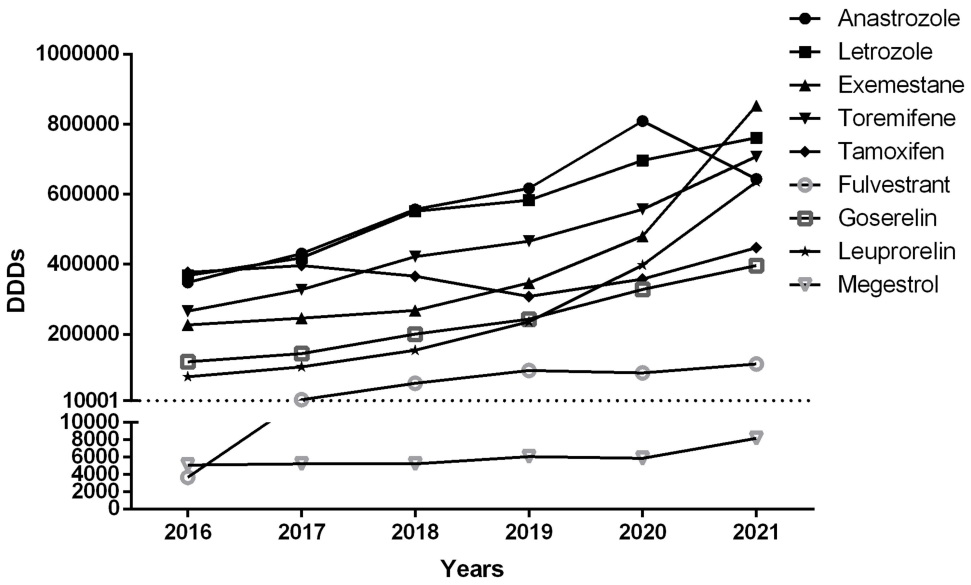

Figure 1 Trends in DDDs of Endocrine Therapy Medications for Breast Cancer (2016–2021).

Table 3 DDC of Endocrine Therapy Medications for Breast Cancer and Their Ranking Across Six Cities in China (2016–2021)

Drugs	2016		2017		2018		2019		2020		2021		
	DDC	Order	DDC	Order	DDC	Order	DDC	Order	DDC	Order	DDC	Order	P
Anastrozole	35.20	4	31.89	4	29.77	4	27.98	4	26.63	4	10.54	5	<0.01
Letrozole	32.58	5	30.11	5	27.64	5	24.95	5	23.76	5	8.95	7	<0.01
Exemestane	42.22	3	40.64	3	37.25	3	33.19	3	32.92	3	33.19	3	0.022
Toremifene	8.88	8	8.46	8	7.92	8	7.69	8	7.69	8	7.53	8	<0.01
Tamoxifen	1.01	9	1.00	9	1.03	9	1.72	9	2.88	9	3.35	9	0.015
Fulvestrant	190.98	1	130.23	1	78.87	1	76.87	1	76.87	1	76.15	1	<0.01
Goserelin	68.37	2	63.87	2	60.56	2	57.77	2	57.58	2	43.61	2	<0.01
Leuprorelin	27.33	6	25.17	6	23.33	6	21.88	6	21.48	6	21.30	4	<0.01
Megestrol	10.58	7	9.36	7	8.53	7	8.68	7	9.13	7	9.03	6	0.348
Total	417.15		340.74		274.89		260.71		258.94		213.65		<0.01

Notes: P, P value for the trend in the DDC, assessed by the Kendall tau-b trend test.

As is shown by the Table 3 and Figure 2, with the exception of megestrol and tamoxifen, the DDC of the other medications exhibited a significant decline over the years ($P < 0.05$). Fulvestrant consistently exhibited the highest DDC among the studied medications, yet it experienced the most substantial absolute decrease in DDC. The DDC of letrozole and anastrozole was situated at a moderate level, and there was a substantial decline in 2021. During the six-year timeframe, the DDC of exemestane maintained a persistent third-place position. The DDC of tamoxifen has consistently been the lowest among the studied medications. However, it has shown an increase over time, with the DDC in 2021 being more than three times that of 2016. Among ovarian function suppression, leuprorelin had a moderate DDC, while goserelin had a relatively high DDC but showed a downward trend by 2021.

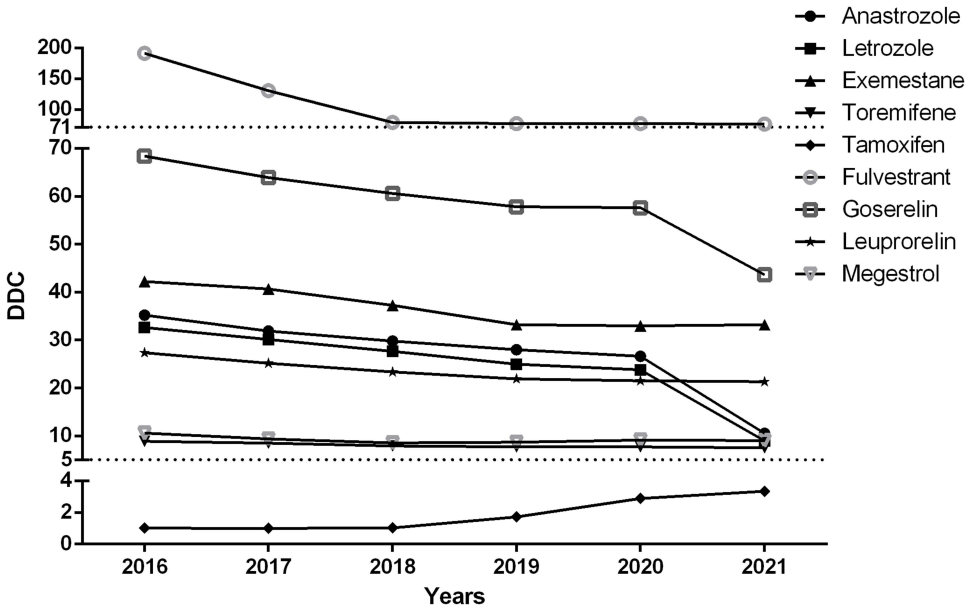

Figure 2 Trends in DDC of Endocrine Therapy Medications for Breast Cancer (2016–2021).

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Table 4 Trends in the Proportion of Dual Drug Combinations for Breast Cancer Treatment (2016–2021)

	2016 (%)	2017 (%)	2018 (%)	2019 (%)	2020 (%)	2021 (%)	P
AI+OFS	6.96	8.03	9.17	10.39	12.53	12.29	0.015
AI+SERDs	0.10	0.12	0.15	0.27	0.17	0.24	0.039
SERMs+OFS	5.92	5.06	5.18	5.28	5.25	5.38	0.573
SERMs+SERDs	0.20	0.14	0.19	0.50	0.10	0.12	0.348

Notes: P, P value for trends in the proportion of dual drug combinations, assessed by the Kendall tau-b trend test.
Abbreviations: AI, aromatase inhibitor; OFS, ovarian function suppression; SERDs, selective estrogen receptor down-regulators; SERMs, selective estrogen receptor modulators.

A Brief Analysis of the Combination Use of Two Drugs

Table 4 illustrates the proportion of patients utilizing both drugs among those who used at least one of the two drugs. The combination of AI and OFS emerged as the most common, with its usage increasing each year ($P < 0.05$). In the pairwise comparisons conducted as part of the analysis of variance (ANOVA), the P-values for the comparisons between 6.96% in 2016 and 12.53% in 2020, as well as between 6.96% in 2016 and 12.29% in 2021, were both less than 0.05 (as depicted in Figure 3). Figure 3 confirms that the AI and OFS combination is the most frequently employed treatment in clinical practice, consistent with current guidelines.

To further explore the reasons behind the notable rise in AI and OFS combination use, patients were categorized into premenopausal and postmenopausal groups based on the age of 50.[17] Table 5 shows that from 2016 to 2021, among the population who have utilized AIs or OFS, the proportion of premenopausal individuals has increased from 19.31% to 29.99%, indicating a trend toward younger age among users of these drugs. Additionally, the proportion of patients using both drugs concurrently rose from 27.60% to 33.27%, demonstrating a shift from single-drug to combination therapy in premenopausal patients. The above two reasons led to an increase in the proportion of combined AI and OFS use in the total population. Incorporating OFS more frequently into treatment plans for premenopausal patients could enhance the standardization of endocrine therapy and improve patient outcomes.[18]

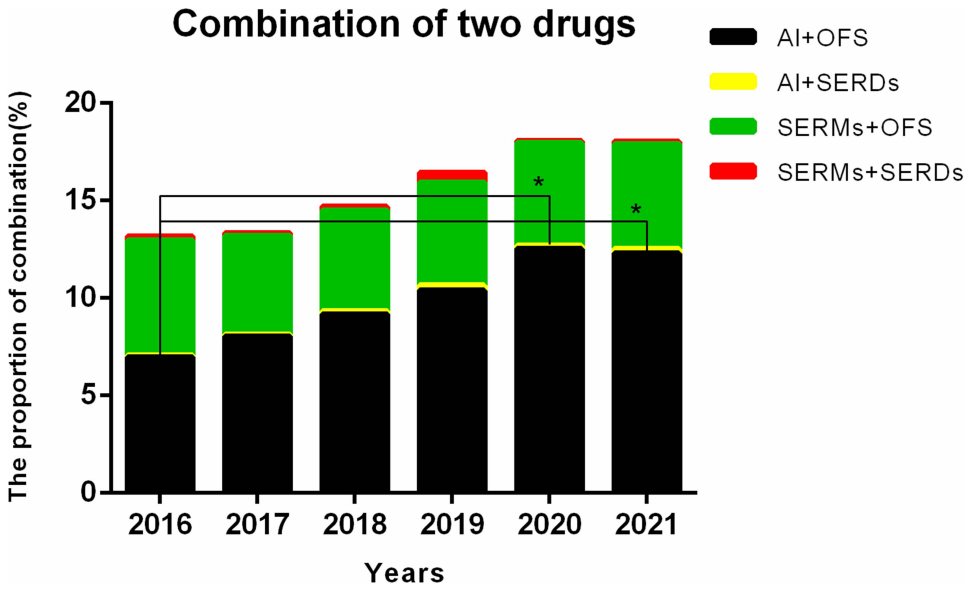

Figure 3 Trends in the Proportion of Dual Drug Combinations for Breast Cancer Treatment (2016–2021). *denotes $P < 0.05$, assessed by multiple comparisons of two-way ANOVA.
Abbreviations: AI, aromatase inhibitor; OFS, ovarian function suppression; SERDs, selective estrogen receptor down-regulators; SERMs, selective estrogen receptor modulators.

Table 5 Comparison of AI and OFS Combination Therapy in Premenopausal and Postmenopausal Patients (2016 Vs 2021)

Took AI or OFS		2016(%)	2021(%)
Pre-menopause	Proportion in the total population	19.31	29.99
	Proportion of combination	27.60	33.27
Post-menopause	Proportion in the total population	80.69	70.01
	Proportion of combination	2.03	3.30

Abbreviations: AI, aromatase inhibitor; OFS, ovarian function suppression.

Discussion

This study analyzed the trends and patterns of combination endocrine therapy for breast cancer across six major cities in China (2016–2021), utilizing a large-scale anonymized database. The total number and costs of prescriptions and DDDs for endocrine therapy drugs were on the rise, indicating that endocrine therapy is increasingly prevalent in clinical settings. Specifically, the prescription volume, prescription costs, DDDs, and DDC of the nine drugs across five categories each exhibited distinct trends.

The prescription volume and associated costs of AI medications are the highest among the drug categories, and their annual DDDs account for approximately 50%, reflecting their most frequent utilization in clinical practice. Concurrently, their DDC were positioned in the mid-range, suggesting that their popularity in clinical practice may be attributed to a combination of favorable therapeutic efficacy and moderate economic burden. This finding is consistent with both guideline recommendations and real-world study outcomes.[19] However, some studies in China have indicated that AI are more cost-effective than tamoxifen,[20] which is inconsistent with our findings. In our study, the DDC of tamoxifen was the lowest over the 6-year period, suggesting that it imposes a smaller economic burden compared to AI. Interestingly, the DDC for tamoxifen in 2021 was three times that of 2016, driven by a significant increase in the drug's unit price (The database of the Hospital Prescription Cooperation Project includes information on the unit prices of medicines). For instance, based on the database studied in this article, the cost of one tablet of tamoxifen rose from 0.39 yuan in 2016 to 1.2 yuan in 2021 in Beijing, more than doubling. Nevertheless, its DDC remains the smallest. However, tamoxifen's DDDs dropped from first place in 2016 to sixth place in 2020, potentially due to the emergence of novel endocrine therapies, or notable side effects.[21] In fact, for premenopausal patients, tamoxifen remains the treatment of choice.[22] Notably, a study has shown that continued use of tamoxifen is associated with superior survival outcomes compared to the combination of AI and OFS, while also demonstrating better cost-effectiveness.[23] Therefore, the utilization of tamoxifen, a cost-effective and efficacious agent, should not be arbitrarily reduced.

In 2021, despite a slight decline in the number of prescriptions, there was a significant reduction in the prescription costs of anastrozole and letrozole. This reduction is consistent with the decrease in the DDC of both drugs in 2021. This decline could be due to a reduction in drug prices from policies like centralized procurement.[24,25] It is likely also attributable to this policy that the DDC of some high-unit-price drugs, such as fulvestrant, goserelin, and leuprorelin, has also experienced a substantial decline. Despite consistently having the highest DDC among the studied medications, fulvestrant underwent the most significant absolute reduction in DDC. The unit price of fulvestrant dropped from over 5000 to above 2000(The data were derived from the raw data within the database). The unit prices of most drugs fell, reducing the economic burden on patients.

Typically, OFS inhibits estrogen secretion in premenopausal women and is therefore primarily used in this group rather than in postmenopausal women.[26] A network meta-analysis concluded that AI+OFS represents the most effective treatment strategy for premenopausal patients.[27] In our study, an increasing number of premenopausal patients were prescribed AI or OFS, with a significant annual increase in the proportion of patients receiving the combination of AI and OFS ($P = 0.015$). In 2021, 33.27% of premenopausal patients were treated with the combined regimen of AI and OFS. Despite this increase, only about one-third of premenopausal patients received combination therapy in 2021. This limited adoption may be due to the need for careful consideration of various factors, including age, tumor size, lymph node status, histological grade, Ki-67 proliferation index,[28] the patient's economic constraints or the side effects of OFS.[29]

For early-stage breast cancer, conservative surgery followed by adjuvant endocrine therapy is recommended for hormone receptor-positive patients. For those with limited life expectancy, basic endocrine therapy is considered a low-risk option.[30] If tumors progress or recur during endocrine treatment, adding targeted therapies can improve efficacy. For instance, CDK4/6 inhibitors are effective in enhancing treatment outcomes.[31] AIs combined with CDK4/6 inhibitors, such as palbociclib and abemaciclib, are preferred for first-line endocrine therapy.[32] This approach is recommended for postmenopausal patients or premenopausal patients after drug-induced ovarian suppression, particularly those with positive sex hormone receptors and negative HER2 receptors. Additionally, attention should be paid to the tumor's immune microenvironment, alongside molecular subtypes. Research into the tumor ecosystem can lead to better treatment outcomes.[33]

This study also has several limitations. The database utilized in this study encompasses only outpatient prescriptions, omitting inpatient prescriptions and failing to capture medication usage information from external pharmacies. Additionally, the data are sourced from six major cities in China, which may introduce sampling bias. Moreover, the dataset lacks information on treatment duration, therapeutic efficacy, and patient adherence. Future research could involve stratifying patients by age for analysis and examining patient adherence to medication as well as long-term patient outcomes.

Conclusions

The use of endocrine therapy drugs is increasingly prevalent in clinical practice, with AI being the most widely used, consistent with guideline recommendations. However, it is recommended that medications like tamoxifen, which are highly cost-effective and also demonstrate good therapeutic efficacy, should be utilized more frequently. The most common combination therapy is AI + OFS. It is suggested that the use of this combination should be increased, based on a comprehensive consideration of factors such as patients' economic burden and drugs' adverse reactions. This study can provide researchers with the basis for further investigation, such as conducting in-depth analyses stratified by age. It can also offer policymakers valuable insights into the cost-effectiveness of medications.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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