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RESEARCH ARTICLE

Off-label use of tamoxifen in a Chinese tertiary care hospital

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Abstract
Background Tamoxifen is an estrogen receptor modulator used for the treatment of breast cancer; however, currently, it is used in many off-label indications. *Objective* To investigate the prevalence of tamoxifen off-label prescribing and explore available scientific evidence that supports those uses in outpatients. *Setting* Xiamen maternity and child health care hospital in Xiamen city of China. *Method* All the prescriptions of outpatients receiving tamoxifen were exported from an electronic prescribing system during a 1-year period. Tamoxifen use was then classified as either on- or off-label according to the criteria we established previously, and the details of the off-label prescriptions were collected. Logistic regression was applied to explore predictive variables. Evidence search was limited to Up-To-Date, the Micromedex database and PubMed. *Main outcome measure* The rate of off-label use, risk factors identified by logistic regression and evidence exhibition. *Results* A total of 75% of all the prescriptions available were classified as off-label use. Hyperplasia of the breast was the most frequently prescribed off-label indication. According to the analysis of logistic regression, male patients, patients less than 34 years old, and physicians with a higher professional title were more likely associated with off-label prescribing. After a search in Up-To-Date, the Micromedex database and PubMed, only male infertility, atypical hyperplasia, mastodynia, peripheral precocious puberty and gynecomastia were found to have strong evidence supporting the use of tamoxifen off-label (22.75%). *Conclusion* Although the off-label use of tamoxifen was common in our hospital, there was a relative shortage of evidence available supporting those uses.

Keywords China · Off-label use · Tamoxifen

Impacts on practice

- Only one-fifth of the off-label indications in this Chinese maternity and child care hospital have scientific evidence that supports its use. These indications are male infertility, atypical hyperplasia, mastodynia, peripheral precocious puberty and gynecomastia.
- Male patients, young patients, and physicians with a higher professional title are risk predictors for the off-label use of tamoxifen.

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Introduction

Tamoxifen, an estrogen receptor modulator, was approved by the Food and Drug Administration (FDA) in 1977 for treatment of patients who exhibit estrogen receptor positive breast cancer [1]. Long term adjuvant tamoxifen treatment for breast cancer patients has been reported to reduce the annual death rate by 31% [2]. In recent years, however, tamoxifen has been used in many ways beyond its approved use, which are so-called 'off-label uses'. Off-label use is the use of a drug with any indication, patient population, route of administration, dosage or treatment regimen that is not listed in the product labeling [3].

There have been several studies that investigated the unapproved uses of tamoxifen [4–7]. Tamoxifen has been found to stimulate gonadotropin secretion and increase testicular function [4], making it an empirical treatment for male infertility. Tamoxifen has also been used for patients with Albright McCune syndrome, which has an initial presentation of precocious puberty, since it can reduce

vaginal bleeding, growth velocity and rate of bone maturation [5]. The mechanism is possibly related to estrogenic effects on bone mineral density and antiestrogenic effects on growth plates [6]. Likewise, tamoxifen can also be an effective option for treatment of gynecomastia in males [7].

Medications are commonly prescribed off-label in medical practice [8–12]. The proportion of off-label use vs FDA approved use in antibiotic prescriptions is estimated to be approximately 40-60% [8–10]. For instance, ceftaroline has been used in some cases for the off-label indication of bone and joint infections, while erythromycin has been used as a digestive prokinetic agent [8]. Antineoplastic medications have also been used off-label in a high proportion of prescriptions, 29–42.9% [11, 12]. However, attention should be drawn on weighing the benefits and risks. Off-label use of prescription drugs has been proven to be associated with adverse drug events, especially when used for those indications that lack strong scientific evidence [13]. When tamoxifen was used off-label, the adverse event profile and frequency varied based on different male populations: gastrointestinal and cardiovascular problems mostly occurred in prostate cancer patients whereas more psychiatric disorders occurred in male breast cancer patients [14].

Three evidence sources, namely, Up-To-Date, Micromedex and clinical practice guidelines, were selected as a result of their evidence-based recommendations to determine the level of scientific evidence for off-label uses of tamoxifen. Up-To-Date is a clinical decision support resource with a rigorous editorial process for evidence-based recommendations [15]. The Micromedex database is an authoritative drug reference that collects common non-FDA approved uses with evaluations of drug efficacy, strength of recommendation, and strength of evidence [16]. Clinical practice guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific circumstances [17] ". The PubMed website [18] was used for retrieval of practice guidelines by specific filters. We reviewed clinical data from all above databases to ensure that no strong scientific evidence was unintentionally omitted.

As far as we know, there is a paucity of studies investigating epidemiological evidence on the extent of tamoxifen off-label use and evidence supporting its outpatient use. The purpose of this study is to make physicians knowledgeable about reliable evidence supporting tamoxifen off-label use, to ensure safe and appropriate use of tamoxifen and restrict off-label use when there is insufficient or weak evidence.

Aim of the study

The aim of the study was to describe the prevalence of off-label tamoxifen prescribing, to identify factors associated with such off-label use and to determine the level of evidence to support such off-label prescribing.

Ethics approval

This study had been approved by the hospital ethics committee with a waiver of informed consent given that only deidentified data were used.

Methods

Study setting and population

This retrospective, cross-sectional study was conducted in a tertiary care hospital located in Xiamen city, China, which has departments of gynecology, obstetrics, pediatric, reproductive medicine, breast surgery clinic, etc. The patient population consists of adult females, children, and a small number of adult males. Although our hospital is a maternity and child health care hospital, some of the outpatient clinics are not limited to females or children, such as general internal medicine and reproductive medicine. A small group of male patients may visit general internal medicine for treatment of upper respiratory tract infection mainly and reproductive medicine for male infertility. Most of the patients come from the southwest area of the Fujian province.

Inclusion criteria

All outpatients who received tamoxifen during a 1-year period from January 1, 2016, to December 31, 2016, were included regardless of sex and age, and accordingly, no sample size limit was used.

Data source

The study data were derived from the Hospital Information System (HIS) software developed by ZOE SOFT Corp. The system was brought into operation in 2004 and includes an electronic prescription system for physicians and pharmacists. All tamoxifen prescriptions were exported from the HIS software and saved in a Microsoft Excel file which contained patient characteristics (name, age, sex, treatment indication and visiting department), drug characteristics (generic name, dosage form, dose,

frequency and route of administration) and physician characteristics (name and professional title). Professional titles of physicians included resident physicians, attending physicians and chief physicians, which were sorted in an ascending order.

Off-label use determination

Whether tamoxifen was used off-label or not was based on the drug label (Shanghai Forward Pharmaceutical Co., Ltd. 2015) [19] that had been approved by the China Food and Drug Administration (CFDA) as of December 2016. According to the CFDA-approved label [19], tamoxifen is approved for recurrent metastatic breast cancer. The on-label usage is 10–20 mg twice per day by oral administration. When the use of tamoxifen was not covered by the label [19], it was classified as 'off-label'. We used the drug label as determining criteria because it is currently the only legally approved on-label document in China. The types of off-label uses were classified into four categories: indication, dosage/frequency, route of administration, and patient population. Off-label use in patient population meant that tamoxifen was used in the population out of indicated age group. If more than 1 indication was written on a prescription, it was determined to be off-label use if any indication was not covered in the label. If multiple dosages or routes occurred, it was determined to be off-label use if one of administrations went outside the scope of the label.

Statistical analysis

The prevalence of tamoxifen off-label use was calculated by the number of off-label prescriptions divided by the total number of tamoxifen prescriptions. The percentage of prescriptions with strong scientific evidence for the off-label use was estimated by dividing the number of off-label prescriptions with strong evidence by the total number of prescriptions off-label for indication.

Logistic regression was performed to explore predictive variables associated with tamoxifen off-label prescribing. The variables for logistic regression were identified according to the method used in a study conducted by Eguale [20], which estimated the association between off-label use and characteristics of patients and physicians. Due to a limitation in the data available, the variables included in our study differ slightly from Equale's study. For example, we excluded the sex of the physician as it has not been associated with off-label use [20]. In our study, age and sex of patients, and professional title of physicians were identified for logistic regression. Statistical analysis was conducted using SPSS software version 23 (IBM Corp).

Level of scientific evidence for off-label indication

The evidence was classified as 'strong' when the use of tamoxifen was recommended by the Up-To-Date website, public clinical practice guidelines, or had a Class I–IIb recommendation level on Micromedex. Additionally, the evidence was classified as 'weak' if the use was not mentioned, not recommended or contraindicated or had a Class III recommendation level on Micromedex.

An adequate evidence search (from January 2000 to September 2017) was conducted through the Up-To-Date website (http://www.uptodatechina.com) [15], Micromedex database (http://www.micromedexsolutions.com) [16] and PubMed website (https://www.ncbi.nlm.nih.gov/pubmed) [18] with filters for practice guidelines incorporated using MeSH terms and synonyms of off-label indications. The MeSH terms included were 'Tamoxifen', 'Hyperplasia', 'Mastodynia', 'Gynecomastia', 'Fibrous Dysplasia, Polyostotic', 'Infertility, Male', 'Fibrocystic breast disease', 'Papilloma, Intraductal', etc.

Breast lumps and nipple discharge exist in both benign and malignant breast disease and were excluded from evidence searches due to a lack of detailed histopathology classification.

Results

A total of 3321 tamoxifen prescriptions (containing 4820 medication orders) and 2088 patients (150 males) who used tamoxifen at least once were identified during the study period. The median patient age was 40 years, ranging from 3 to 75 years. The prescriptions were written by 24 physicians from 5 outpatient clinics (breast clinic, gynecology clinic, pediatric clinic, reproductive medicine center and general internal medicine clinic). The number of male and female physicians was equal. Attending physicians constituted the majority of the included physicians (n = 11; 45.93%), followed by chief physicians (n = 8; 33.33%) and resident physicians (n = 5; 20.83%).

Approximately 75% (2502 prescriptions) of all the prescriptions available were classified as off-label use. Of those, 2242 prescriptions were used for an off-label indication. The most frequent off-label prescribing indication was hyperplasia of the breast which represents 49.15% (1102 prescriptions) of all the prescriptions for off-label indication. This was followed by the indications of breast lumps (483 prescriptions) and breast cysts (243 prescriptions). The common off-label indications, those with a prescribing frequency of more than 5, are shown in Table 1. In total, 607 prescriptions and 1918 prescriptions were associated with off-label doses (single dose < 10 mg) and off-label frequencies (once per day) during treatment, respectively.

Table 1 Tamoxifen off-label use by indication with prescribing frequency of more than 5 and summary of evidence at UpToDate, Micromedex and published guidelines

Off-label indication	No. of prescriptions off-label for each indication (%)[a]	UpToDate[b]	Micromedex[c]	Guidelines[d]
Sclerosing adenosis	70 (3.12)	Not recommended	Benign breast diseases	Not recommended [26]
Breast cyst	243 (10.84)	Not recommended	Efficacy	Not recommended [26]
Hyperplasia of the breast	1102 (49.15)	Not recommended	Adult, evidence favors efficacy	Not recommended [26]
Intraductal papilloma	36 (1.61)	Not recommended	Recommendation	Not recommended [26]
Fibrocystic breast disease	11 (0.49)	Not recommended	Adult, Class IIb	Not recommended [26]
Atypical hyperplasia of the breast	122 (5.44)	Recommended, for it can reduce the risk of breast cancer	Strength of evidence: adult, category B	Recommended, for it can reduce the risk of breast cancer [26, 35–37]
Mastalgia	230 (10.26)	Recommended, for it provide breast pain relief	Efficacy: adult, evidence favors efficacy	Recommended, for it demonstrate reduction of breast pain [26, 38]
			Strength of recommendation: adult, class IIb	
			Strength of evidence: adult, category B	
Gynecomastia	6 (0.27)	Recommended, for it is considered as a brief trial for relief of tenderness.	Efficacy: adult, evidence favors efficacy; pediatric, evidence favors efficacy	N/A
			Recommendation: adult, class IIb; pediatric, class IIb	
			Strength of evidence: adult, category B; pediatric, category B	
Peripheral precocious puberty (Albright McCune syndrome)	8 (0.36)	Decrease the vaginal bleeding episodes and slow the rate of bone age advancement	Efficacy: pediatric, evidence favors efficacy	N/A
		There is no clear recommendation	Recommendation: pediatric, class IIb	
			Strength of evidence: pediatric, category B	
Male infertility	144 (6.42)	Increase pregnancy rates, sperm concentration and sperm motility	Efficacy: adult, evidence favors efficacy	Lead to some improvement in sperm quality and spontaneous pregnancy rates
		There is no clear recommendation	Recommendation: adult, class IIb	No clear recommendation is made [39]
			Strength of evidence: adult, category B	
Breast lumps	483 (21.54)	Not implemented[e]	Not implemented	Not implemented
Nipple discharge	13 (0.58)	Not implemented	Not implemented	Not implemented

[a]The percentage was the proportion of each off-label indication calculated by dividing the number of prescriptions with each certain indication by total number (2242) of prescriptions off-label for indication. For example, the proportion of prescriptions with off-label indication of "sclerosing adenosis" was calculated by equation "70 × 100%/2242 = 3.12%"

[b]Available from: http://www.uptodatechina.com

[c]Available from: http://www.micromedexsolutions.com

[d]Available from: https://www.ncbi.nlm.nih.gov/pubmed

[e]Breast lumps and nipple discharge exist in both benign and malignant breast disease and were excluded from evidence searches due to a lack of detailed histopathology classification

Logistic regression analysis suggested that male patients, patients aged less than 34, and physicians with higher professional title (attending physicians and chief physicians) were more likely to prescribe off-label prescriptions (Table 2). There were no breast cancer cases in the male patients in our study, so all of these patients received off-label tamoxifen treatment. Young patients (age ≤ 34) received the most off-label treatments, followed by patients ≥ 60 years old [odds ratio (OR) 0.47, 95% confidence interval (CI) 0.22–0.99] and 35–59 years old (OR 0.67, 95% CI 0.57–0.79). More off-label prescribing occurred when the prescriber was a chief physician (OR 2.24, 95% CI 1.78–2.80) or an attending physician (OR 1.41, 95% CI 1.12–1.77) compared to resident physicians.

Of all the off-label indications, only 5 (male infertility, atypical hyperplasia, mastodynia, peripheral precocious puberty and gynecomastia) had strong evidence supporting their use (Table 1). There was no strong evidence available to support tamoxifen for accessory breast tissue. The proportion of prescriptions with strong evidence-based indications was lower (22.75%, 510 prescriptions) than the proportion with weak evidence-based indications.

Discussion

This retrospective analysis demonstrated a very high prevalence of off-label tamoxifen use, accounting for up to 75% of tamoxifen prescriptions at a tertiary care hospital. Hyperplasia of the breast was the most common off-label indication. Among all off-label uses, only one-fifth (22.75%) of the prescriptions had strong evidence.

There might be two reasons to explain the high rate of off-label use. First of all, it's the difference of approved indication between FDA and CFDA that partially causes the high rate of off-label use. Based on the Gail model, tamoxifen is used for chemoprevention of breast cancer when used in the patients with certain type of benign breast disease (atypical hyperplasia of the breast) along with other risk factors, which was approved by the FDA in 1999 [21, 22]. In China, however, chemoprevention of breast cancer was unlicensed by CFDA at the time of this study, because there has been no relevant study in the Chinese population submitted for the evaluation of this indication and the Gail model has been proven to not be suitable for Asian patients [23, 24]. This led to tamoxifen used for chemoprevention of breast cancer being classified as off-label use in our study according to the off-label determination criteria, and therefore increased the rate of off-label use. In addition, given that there is no drug with on-label indication for chemoprevention of breast cancer by CFDA, off-label use of tamoxifen may be the optimal choice for physicians at present, subsequently resulting in the high rate of off-label use.

The low rate of strong scientific evidence supporting among off-label prescriptions is due to a large amount of prescriptions of benign breast disease with a low breast cancer risk, such as hyperplasia of the breast, which lacked strong evidence. The difference of risk in developing breast

Table 2 Logistic regression models of factors associated with tamoxifen off-label use

	Off-label prescriptions, n[a] (%)[b]	On-label prescriptions, n (%)	Total prescriptions, n	Adjust OR[c]	95% CI[d]
Prescribing according to patient sex					
Female	2352 (74.17%)	819 (25.83%)	3171	1 [Reference]	
Male	150 (100%)	0 (0%)	150	1.48	1.20–1.96
Prescribing according to patient age group					
≤ 34 years	889 (90.43%)	94 (9.57%)	983	1 [Reference]	
35–59 years	1597 (68.98%)	718 (21.02%)	2315	0.67	0.57–0.79
≥ 60 years	16 (69.57%)	7 (20.43%)	23	0.47	0.22–0.99
Prescribing according to physician professional title					
Resident physicians	186 (50.96%)	179 (49.04%)	365	1 [Reference]	
Attending physicians	937 (66.60%)	470 (33.40%)	1407	1.41	1.12–1.77
Chief physicians	1379 (89.03)	170 (10.97%)	1549	2.24	1.78–2.80

[a]The "n" meant the number of prescriptions in each category. The analysis in Table 2 was prescription-based rather than person-based

[b]The percentage was calculated by dividing the number of off-label or on-label prescriptions by total number of prescriptions in each subgroup. For example, in the subgroup of prescriptions of which patients aged between 35 and 59 years, the percentage of off-label prescriptions was calculated by equation "1597 × 100%/(1597 + 718) = 68.98%"

[c]*OR* Odds ratio

[d]*CI* confidence interval

cancer was variable among different types of benign breast disease which include non-proliferative lesions (breast cyst), proliferative lesions without atypia (hyperplasia of the breast, sclerosing adenosis and intraductal papilloma) and proliferative lesions with atypia (atypical hyperplasia of the breast). Compared to the general population, the risk of developing breast cancer in proliferative lesions without atypia was 1.3- to 1.9-fold, whereas this risk in proliferative lesions with atypia was 3- to 6-fold [25]. In response, *The American College of Obstetricians and Gynecologists* (ACOG) guidelines [26] recommend tamoxifen use for primary chemoprevention in women with atypical hyperplasia, which had a 1.7% or greater 5-year risk of developing breast cancer, not in women with a low breast cancer risk.

As was shown in the multivariate logistic regression (Table 2), male patients, patients < 34 years old, and physicians with a higher professional title (chief physicians and attending physicians) were determined as the predictor variables associated with off-label prescribing. The likely explanations for those finding are the following: male breast cancer incidence is much lower than female, with a female-to-male incidence rate ratio of 122:1, according to a global investigation [27]. During our study period, there was no male breast cancer indication identified. It is obvious that male patients administrating tamoxifen tend to receive off-label prescriptions. In China, the mean age at diagnosis of breast cancer is 45–55 years [28], so younger patients had a higher chance of receiving tamoxifen treatment for indications other than breast cancer, such as benign breast diseases, which begins to rise in patients between 10 and 19 years old [25]. For the distinction on the rates of off-label prescribing between physicians with high and low professional titles, it was hypothesized that chief physicians and attending physicians make clinical decisions more likely based on medical experience or on drug information obtained from drug company representatives [29].

A previous investigation by Kahan [30] found that in Israel only 5.8% of tamoxifen off-label prescribing occurred in a managed care population. Moreover, the off-label indications, mainly consisting of malignant neoplasm of ovary (13/41) and female infertility (5/41), also differed from our study. The distinction of the outcomes between the two studies is probably related to hospital settings and disease management models. In addition, the differences in the definition of off-label use could also be attributed to the result deviations.

Differing from several previous studies [30–33], our study added Up-To-Date as another source to provide more information for the assessment of off-label use. Although in this study we increased the number of sources used to determine whether or not there was strong evidence, only 21.06% of all off-label prescriptions had strong evidence for their respective indications. The indications with strong evidence were male infertility, atypical hyperplasia, mastodynia, peripheral precocious puberty and gynecomastia. It is still challenging to improve physician prescribing practices with regards to the use of tamoxifen. For solving the problem, it is suggested that physicians should be requested to apply for permission of off-label use, which would be approved or not by pharmacy administration committee, depending on whether or not it is supported by strong evidence. If approved, tamoxifen off-label use can be prescribed routinely and patients receiving off-label use should be informed the benefit and risk of this practice. In contrast, off-label prescribing without strong evidence should be restricted or even forbidden by information technology or administrative measures.

The cost of each tablet of tamoxifen is 0.47¥ ($0.069) in China and is paid by public health insurance regardless of on-label or off-label indications. It had been found that extended tamoxifen use was more cost-effective for the treatment of postmenopausal women with hormone receptor positive breast cancer than the standard tamoxifen regimen [34]. However, there was limited data for the cost-effectiveness of tamoxifen when used off-label. Our study had provided some off-label indications with strong evidence for further cost-effectiveness investigations and can contribute to health insurance decision making.

Several limitations also should be noted in our study. At data collection stage, we found that physicians possibly prescribed tamoxifen to some of patients for breast cancer prevention before the results of histopathologic examination came out. Those patients would be diagnosed as hyperplasia of the breast, which may underestimate the proportion of atypical hyperplasia of the breast and subsequently affect the accuracy of rate of off-label prescriptions with strong evidence. In addition, the results should not be extrapolated to other comprehensive hospitals because the rate of off-label prescribing may be different in various patient populations. Finally, the sources of evidence were restricted to only decision support systems (Up-To-Date and Micromedex) and published clinical guidelines, resulting in a possible underestimation of available evidence which might be derived from some primary studies and ongoing trials.

Conclusion

Based on the electronic prescribing system, we found a high prevalence of tamoxifen off-label prescribing and most of the off-label indications were not supported by strong evidence. There is an urgent need for more clinical trials to further assess the risks and benefits of tamoxifen off-label use, which would subsequently provide information for clinical decision making.

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