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# The impact of tamoxifen brand switch on side effects and patient compliance in hormone receptor positive breast cancer patients

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ABSTRACT

*Background:* In 2006 Nolvadex was discontinued and replaced by a variety of alternative generic tamoxifen brands for the adjuvant treatment of breast cancer. Anecdotally, patients are switching brands and taking alternative medications to reduce treatment related symptoms. Nevertheless, more severe side effects may equate to better relapse prevention. This study evaluates generic tamoxifen adherence and its correlation with side effects and brand switch.

*Methods:* Consecutive disease free ER positive patients (stage I–III) were invited to respond to a questionnaire. 165 of 327 questionnaires were returned (50% response). Pearson's Chi Square test was used for data analysis.

*Results:* 63 patients (38%) reported a switch between generic tamoxifen. 59% of all patients experienced side effects associated with tamoxifen treatment of which 53% were severe. Patients experiencing differential symptoms dependent on tamoxifen brand reported more severe side effects ($p = 0.02$). Non-prescribed supplements were taken by 42% of all patients with no significant improvement in climacteric symptoms ($p = 0.05$). The concomitant use of SSRIs appeared to have no effect on symptoms. A significant number of patients considered discontinuing tamoxifen because of the side effects ($p = 0.001$), yet this did not translate into discontinuation or non-adherence ($p = 0.8$ and 0.08 respectively).

*Conclusion:* Severe tamoxifen side effects are commonly experienced by breast cancer patients and can be significantly altered by change in tamoxifen brand.

Most patients will continue to take tamoxifen, despite side effects to avoid cancer relapse. Supplementation and antidepressants did not improve tamoxifen related side effects in our cohort.



## Introduction

Endocrine manipulation for the systemic treatment of breast cancer had been used since its first description by Beatson in 1896 [1]. Tamoxifen, a selective oestrogen receptor modulator, was first used in 1969 and had been the hormonal therapy drug of choice before the introduction of 3rd generation aromatase inhibitors (AI). Tamoxifen is the first line endocrine agent for the treatment of oestrogen receptor positive breast cancer in pre- and peri- menopausal women [2,3]. It is also used for women unable to tolerate aromatase inhibitors, those with low risk breast cancer requiring osteoporosis prevention, as primary medical therapy, for chemoprevention and after failure of other endocrine agents.

While the use of tamoxifen and the AIs may benefit many breast cancer patients and women at high risk of the disease, these drugs have also been shown to cause bothersome side effects in a significant proportion of women leading to withdrawal from treatment in up to 30% of patients [3,4]. Though the overall occurrence of side effects is slightly lower among women who take tamoxifen rather than AIs, the impact of side effects on quality of life can be severe enough for some to stop their medication. Despite the proven effectiveness and acceptable tolerability profiles of endocrine treatment, their adverse effects are not only variable, but also underestimated [4–6]. Interestingly, more pronounced side effects associated with endocrine treatment tend to be interrelated with better outcomes [7–9].

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The introduction of several generic tamoxifen preparations leading to switches between treatments could have implications on patients' side effects and compliance. In addition, such medication switch could introduce an element of uncertainty between patients and their doctors. We have seen good anecdotal evidence that the side effects and tolerance of tamoxifen varies with brand type. A small series of patients have reported differing symptoms with alternative brands that ceased on stopping and recurred on restarting individual preparations. These generic preparations may have differing bioavailability despite all containing 20 mg tamoxifen citrate as they contain very different excipients (Table 1). They therefore may have varying tolerability and potency in preventing relapse. Patients may also select the brand that gives least side effects unaware that they may therefore get less protection from cancer relapse.

Many patients resort to non-prescribed supplements, and a smaller proportion are prescribed anti-depressants (including SSRIs) for tamoxifen related side effects. Absorbed tamoxifen is metabolised by the CYP2D6 in the liver. To date, there is some evidence that heterogeneity in the CYP2D6 genome could affect the efficacy of tamoxifen treatment of breast cancer, and therefore drugs that are moderate and strong inhibitors of CYP2D6 should not routinely be co-prescribed with tamoxifen [10–13]. It is unclear whether tamoxifen switch in breast cancer patients on adjuvant endocrine treatment can be linked to such trends as a result of altered side effects.

This study aims to evaluate changes in side effects reported by patients switching from one generic Tamoxifen brand to another, and whether such change in the side effects affect adherence to treatment. To provide an understanding of possible correlations between anti oestrogen treatment side effects and other factors associated with discontinuation and non adherence to hormonal therapy, we devised a questionnaire to investigate the prevalence of the varying side effects of different tamoxifen brands, the decisions patients made in managing side effects and any confounding co-prescriptions. We compared the rates and predictors of discontinuation and non-adherence for tamoxifen over a 2-year period in women treated for oestrogen receptor (ER) positive breast cancer in the Royal Hampshire County Hospital (RHCH). We focused on the type and severity of symptoms and confounding variables such as co-prescription of CYP2D6 inducers in these patients.

## Methods

### *Sample selection*

The RHCH breast unit database (BASO II) was interrogated for all disease free, oestrogen receptor positive, early breast cancer patients (stage I–III) between January 1, 2007 and December 31, 2009. We restricted our cohort to patients who have received at least one prescription for oral hormonal therapy within the first year of diagnosis.

### *Data collection, follow up and censoring*

Questionnaires were sent out to 327 eligible patients. Patients who received an aromatase inhibitor only as their primary hormonal therapy were excluded. Patients discontinuing therapy along with patients restarting treatment after 90 days were categorised in the discontinuation group and those who stopped treatment for less than 28 days were classified in the drug holiday group.

The questionnaire specifically investigated the patients' experience of common menopausal symptoms, whether they took supplements and whether that changed their symptoms. They were asked to list medicines co-prescribed with tamoxifen especially antidepressants. Patients were also asked if they had considered stopping tamoxifen because of the side effects, what made them continue hormonal therapy. Participants were also asked if they had ever had a drug holiday and if they had permanently stopped treatment because of side effects. We also enquired if patients had noticed that there were different tamoxifen preparations and if these made any difference to their symptoms.

### *Statistical analysis*

Associations between tamoxifen brands, supplements and other medications to side effects and adherence to hormonal therapy were analysed using the Pearson Chi-Square Fisher's Exact tests. Two-sided statistical tests with an alpha level of 0.05 were performed using SPSS (version 201.0.0).

**Table 1**
The different tamoxifen brands and excipient components, which could contribute to variable absorption, side effects and efficacy.

| | Wockhardt | APS | Soltamox | RelonChem | Milpharm |
|---|---|---|---|---|---|
| Lactose | ✓ | × | × | × | × |
| Maize starch | ✓ | × | × | × | × |
| Pregelatinised maize starch | ✓ | × | × | × | × |
| Magnesium stearate | ✓ | ✓ | × | ✓ | ✓ |
| Methylhydroxypropylcellulose | ✓ | × | × | × | × |
| Propylene glycol | ✓ | × | ✓ | × | × |
| E171 | ✓ | ✓ | × | × | × |
| E464 | ✓ | × | × | × | × |
| Mannitol | × | ✓ | × | × | × |
| Povidone | × | ✓ | × | ✓ | ✓ |
| Sodium starch glycolate | × | ✓ | × | ✓ | ✓ |
| Colloidal silicon dioxide | × | ✓ | × | × | × |
| Hypromellose | × | ✓ | × | × | × |
| Polyethylene glycol | × | ✓ | × | × | × |
| Ethanol | × | × | ✓ | × | × |
| Glycerol (E422) | × | × | ✓ | × | × |
| Sorbitol (E420) | × | × | ✓ | × | × |
| Natural aniseed flavouring | × | × | ✓ | × | × |
| Liquorice flavouring | × | × | ✓ | × | × |
| Calcium hydrogen phosphate | × | × | × | ✓ | ✓ |
| Microcrystalline cellulose | × | × | × | ✓ | ✓ |
| Colloidal anhydrous silica | × | × | × | ✓ | ✓ |