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Original article

Prevalence of the co-prescription of tamoxifen and CYP2D6 inhibitors in Saudi population: A cross sectional study

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ABSTRACT

Consumption of Cytochrome P450 2D6 (CYP2D6) inhibiting drugs along with tamoxifen treatment results in decrease in plasma concentration of endoxifen, the major active tamoxifen metabolite. Simultaneous use of CYP2D6 inhibitors, such as selective serotonin reuptake inhibitors (SSIs), as well as lesser tamoxifen adherence may negatively impact tamoxifen efficacy in patients with breast cancer. The objective of our study was to assess the co-prescription of CYP2D6 inhibitors and tamoxifen use and also to relate concomitant CYP2D6 inhibitor use and tamoxifen adherence to breast cancer in Riyadh, Saudi Arabia. All patients treated for breast cancer who had at least one tamoxifen prescription in their electronic medical records (EMRs) from June 2015 to June 2017 were included. Patients who had other adjuvant hormonal therapy were excluded from the study. In total, 499 patients (25 males and 474 females) with breast cancer using tamoxifen were included. Our study was purely observational study revealed that prescription of weak inhibitors with tamoxifen increased in the second year as opposed to decrease in the prescription of strong inhibitors. Also, a substantial percentage of patient population were found to be non-adherent to the tamoxifen therapy in this study.

1. Introduction

Breast cancer is one of the most aggressive and frequently diagnosed non-cutaneous malignancy occurring in women worldwide (Alotaibi, 2018; Siegel, 2019). According to the American Cancer Society signs like change in breast size, lump in the breast, fluid discharge from the nipple and pain are indications of breast cancer (Alotaibi, 2018). Life style, age, familial history and genetic predisposition are the common factors that influence the chances of developing breast cancer. The prevalence of breast cancer among Saudi women is 29% making it common malignancy among women in the kingdom (Alsolami, 2019). The recent survey conducted by El Bcheraoui et al. (2015) for cancer related mortality among Saudi women reveals that breast cancer is the 9th most common cause of death (Lozano et al., 2012).

Tamoxifen, is a United States Food and Drug Administration (US-FDA) and Saudi FDA approved selective estrogen receptor modulator (SERM) that is used to reduce recurrence of breast cancer after surgery or radiation (Clemons et al., 2002). It is indicated for the treatment and prevention of breast cancer in patients with greater risk of developing such cancer. It is approved for the use in high risk patients as prophylaxis and as an adjuvant therapy with dose ranges from 20 to 40 mg orally daily for a period of 3–5 years (Fisher et al., 2005; Laboratories, 2011; Hagen et al., 2019). Tamoxifen acts by blocking estrogen receptor on breast cancer tissue and consequently preventing their growth. Therefore, it is used in estrogen positive tumors which constitute about 25% to 33% of breast cancer tumors (Anderson et al., 2002; Anderson et al., 2011; Al-Tamimi et al., 2010).

In the human body, tamoxifen needs to be metabolized by certain liver enzymes, cytochrome P450 (CYPs), to yield more potent metabolites (Ratliff et al., 2004; Wisniewska et al., 2016; Sanchez-Spitman et al., 2019). The main CYP responsible for metabolism of tamoxifen is CYP2D6 enzyme, it metabolizes tamoxifen

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to endoxifen (4-hydroxy-N-desmethyl-tamoxifen), which is reported to be hundred times more potent than tamoxifen. Also endoxifen is chiefly responsible for exerting its action on breast cancer tumors (Higgins and Stearns, 2011; Sanchez-Spitman et al., 2019). Moreover, endoxifen needs to exceed certain concentration level in blood in order to be effective (Hawse et al., 2013). Nevertheless, tamoxifen has notable side effects such as night sweats and hot flashes (Ratliff et al., 2004; Wiśniewska et al., 2016). Those side effects can be quite bothersome to the patients. In fact, Incidence of hot flashes can range from 50% to 80% of patients treated with tamoxifen. Owing to these side effects many patients may be at risk of breast cancer recurrence due to poor adherence and higher discontinuation rate which is associated with worsening treatment outcomes (Lash et al., 2006; McCowan et al., 2008; Dezentje et al., 2010; Mom et al., 2006).

To overcome these side effects certain antidepressants are prescribed to alleviate those side effects such as selective serotonin reuptake inhibitors (SSRIs). As much as quarter of patients experiencing those side effects are considered for SSRIs treatment (Love, 2005; Desmarais, 2010). The problem with SSRIs, among other drugs that are prescribed for decreasing tamoxifen induced side effects, is that they can decrease endoxifen plasma level by preventing tamoxifen metabolism through inhibition of CYP2D6 enzyme (Lammers et al., 2010). Their degree of inhibition varies depending on the medication from strong to weak inhibitors (Ratliff et al., 2004). The degree of inhibition is based on FDA classification which categorizes strong, weak and moderate inhibitors. A Strong inhibitor is one that causes a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance. A Moderate inhibitor is one that causes a >2-fold increase in the plasma AUC values or a 50–80% decrease in clearance. A Weak inhibitor is one that causes a >1.25-fold but <2-fold increase in the plasma AUC values or a 20–50% decrease in clearance (Drug Development and drug interactions, US-FDA 2019; Guidance's on drugs, US-FDA 2018; Drug interaction flock chart table, Indiana University, 2019). CYP2D6 inhibition leads to greater risk (13.6%) of breast cancer recurrence in patients who are on tamoxifen therapy and are simultaneously taking CYP2D6 inhibitors (Aubert et al., 2009). US-FDA advisory committee in its recommendations on October 2006 asked pharmaceutical companies to change the label of tamoxifen, mentioning that postmenopausal ER-positive breast cancer (Estrogen receptor) patients who are poor CYP2D6 metabolizers by genotype or due to drug interactions may be at higher risk of breast cancer recurrence. Many practitioners switched to prescribing other medications that do not interact with tamoxifen metabolic pathway, such as gabapentin, for alleviating those side effects such as hot flashes (Pandya et al., 2005). However, no such report about co-prescription of CYP2D6 inhibitors with tamoxifen has been reported in Saudi Arabia. Dusetzina et al. (2013) reported that in united states, 24% of women using tamoxifen between 2004 and 2010 in any given month also received a prescription for an antidepressant within that same month. 34% were prescribed strong inhibitors during the first 2 years of observation. By 2010, strong inhibitors were used in 15% of women co-prescribed tamoxifen. In Netherlands, 14% of women who received tamoxifen between 2005 and 2010 also received one of the following antidepressants namely paroxetine, fluoxetine, sertraline, fluvoxamine, citalopram, escitalopram, and venlafaxine (Binkhorst et al., 2013). Around 80.9% of those women received regular antidepressant treatment with tamoxifen (concomitant use for at least 90 days). In Belgium between 2006 and 2009, 7.02% of women taking tamoxifen also received one CYP2D6 inhibitor from March through April of 2006 (Dieudonne et al., 2014). This percentage was reduced to 5.73% in July–August of 2009.

To our knowledge no study has been performed in Riyadh population to assess prevalence of co-prescription of tamoxifen therapy along with CYP2D6 inhibitors. The main aims of this study were to explore the effects of associated CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in patients treated with adjuvant tamoxifen in population of Riyadh, Saudi Arabia.

2. Materials and methods

This was a descriptive retrospective cross-sectional study. Pharmacy data were obtained and reviewed from two major hospitals in Riyadh, Saudi Arabia. Data from King Saud University Medical City (KSUMC), a tertiary care and referral hospital with more than 1000 bed capacity, and Prince Sultan Military Medical City (PSMMC) were reviewed to look for any hormonal therapy prescriptions of tamoxifen. All patients who had at least one tamoxifen prescription in their electronic medical records (EMRs) from June 2015 to June 2017 were included. Patients who had other adjuvant hormonal therapy were excluded from the study. Retrieved data from EMRs included patients demographic characteristics: age and sex. Categorizing CYP2D6 inhibitors was referenced based upon US-FDA website into the following categories (according to examples of clinical inhibitors for P450-mediated metabolisms table): strong that caused a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance (fluoxetine, paroxetine, terbinafine, bupropion and quinidine) moderate is the one that causes a >2-fold increase in the plasma AUC values or a 50–80% decrease in clearance. (fluvoxaminec, imetidine, cinacalcet, mirabegron and duloxetine), and weak is one that causes a >1.25-fold but <2-fold increase in the plasma AUC values or a 20–50% decrease in clearance (abiraterone, amiodarone, cimetidine, celecoxib, clobazam, cobicistat, escitalopram, lorcaserin, ritonavir, sertraline, vemurafenib, desvenlafaxine and labetalol) (Drug Development and drug interactions, US-FDA 2019; Guidance's on drugs, US-FDA 2018; Drug interaction flock chart table, Indiana University, 2019). After that, a matching was done between those drugs and drugs in EMRs of patients on tamoxifen to find which CYP2D6 inhibitor was prescribed concomitantly with tamoxifen during the study period. To assess the adherence of tamoxifen (the percentage of filled medication by the patient from whole prescribed amount) in one year, patients who received tamoxifen twice and had 12 or more months separating those two entries were included. This ensured that all included patients received tamoxifen for at least one year (Wu et al., 2015). Next, 12 months were counted starting from the first entry and labeled this year Measured Year (MY). Since tamoxifen is taken daily the number of days of supply in the record will indicate the fraction of a year when patient had coverage for tamoxifen, i.e. patient or caregiver were adherent to present to the pharmacy to fill the medication. The following equation was used to calculate primary adherence:

$$\textit{Primary adherence } (\%) = \frac{\textit{Days of supply in MY}}{365} \times 100$$

3. Results

A total of 499 patient's received tamoxifen prescriptions (Table 1). Only 25 males received tamoxifen during this period

Table 1
Tamoxifen prescription and number of patients per year.

	First year	Second year	Total
No. of prescriptions (%)	535 (41.73)	747 (58.27)	1282 (100)
No. of patients (%)	209 (41.88)	290 (58.12)	499 (100)

and the majorities were females (Table 2). There was change in the mean age of patients who received tamoxifen in the second year (45.15 ± 11.62 years) as compared to the first year (43.32 ± 10.96 years). The identified strong CYP2D6 inhibitors that were co-prescribed with tamoxifen included only Bupropion. No moderate inhibitors were identified during the study period. The co-prescribed weak inhibitors included: escitalopram, sertraline, celecoxib, and venlafaxine. Figs. 1 and 2 show the prevalence of co-prescription of tamoxifen with CYP2D6 inhibitors in the first and second year of the study period, respectively. Fig. 3 represents the adherence for patients who received tamoxifen for 12 or more months. 171 patients used tamoxifen for duration of ≥12 months (34.26%). 30% of these patients had an adherence of <85%. A subgroup analysis of KSUMC patients revealed that two of the three males who filled tamoxifen from hospital pharmacy were diagnosed of breast cancer and one didn't have any indications in his EMR for tamoxifen therapy (n = 3). The majority of females in KSUMC (n = 131, 98.5%) had diagnosis of breast cancer regardless of the stage. One female had ovarian cancer (0.75%) and one didn't have any indications for tamoxifen treatment (0.75%).

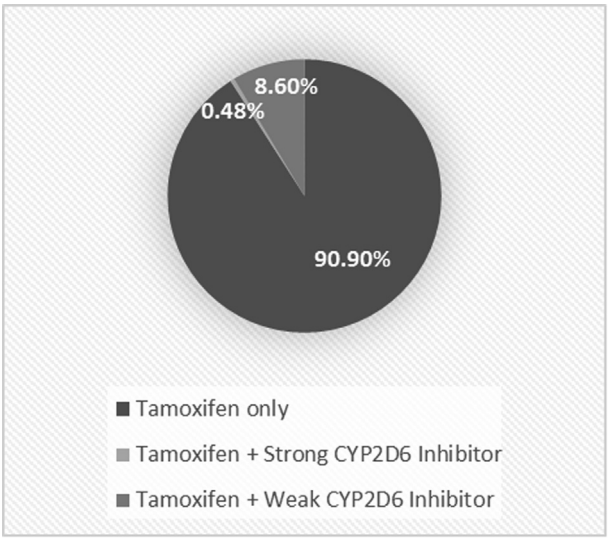

Fig. 1. Co-prescription of tamoxifen with CYP2D6 inhibitors in first year (n = 209).

4. Discussion

This study focused on documenting the prevalence of co-prescription of tamoxifen with CYP2D6 inhibitors as well as the adherence to tamoxifen therapy. Knowing that, researchers can come up with strategies to improve adherence and reduce this co-prescription. In a two-year period, the mean age increased in patients who were prescribed tamoxifen in two major hospitals in Riyadh. There was minimal co-prescription of tamoxifen with corresponding strong CYP2D6 inhibitors. However, the prescription of weak inhibitors with tamoxifen increased in the second year as opposed to decrease in the prescription of strong inhibitors. Approximately, third of patients who were determined to have had tamoxifen for one or more year had adherence of <85%. The fact of the breast cancer epidemiology is that women diagnosed with breast cancer are more of old age and post-menopausal than young women (Tamimi et al., 2016; American cancer Society, 2017). This group of women might be of potential greater risk of cancer recurrence when having tamoxifen-CYP2D6 interaction according to US-FDA advisory (Goetz et al., 2008; Dean, 2019). Thus, the age and menopausal status should be taken into consideration when prescribing any CYP2D6 inhibitors. Although the co-prescription of strong inhibitors decreased in the second year of the study, there is actually overall increase in the percentage of co-prescription as it closes to 10% in the second year. In the US study (Dusetzina et al., 2013) the percentage of co-prescription at any given month between 2004 and 2010 was 24% with average absolute 1.5 reductions yearly until it reached 15% in 2010. If reduction rate is kept the same, this will result in co-prescription of only 3% in 2018. Applying the same principle to the Belgium study (Dieudonne et al., 2014) percentage of co-prescription and it will be found that with 0.43 absolute yearly reductions the percentage was reduced from 7.02% to 5.73%. This means that if reduction rate were unchanged this percentage would have reached 1.88% in 2018.

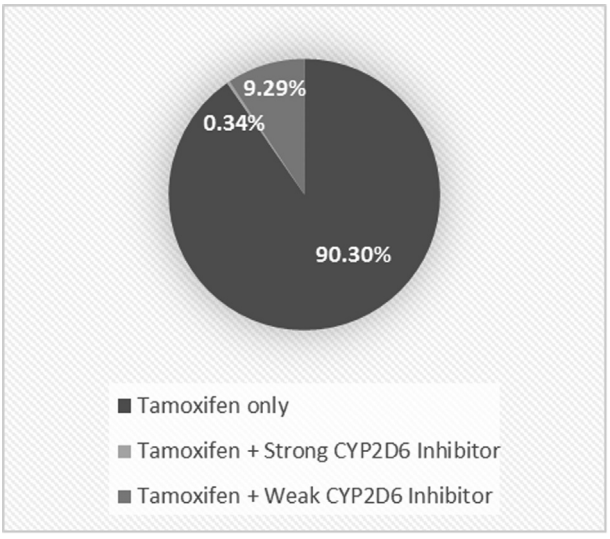

Fig. 2. Co-prescription of tamoxifen with CYP2D6 inhibitors in second year (n = 290).

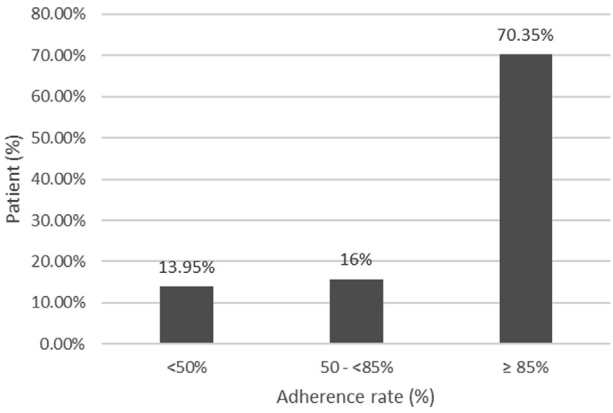

Fig. 3. Overall adherence percent of patients in three different subgroups based on adherence rate.

Table 2
Demographic characteristics (M: Male, F: Female).

	First year (n = 209)	Second year (n = 290)
Gender		
M	2.87% (6)	6.55% (19)
F	97.13% (203)	93.45% (271)
Age ± SD	43.32 ± 10.96	45.15 ± 11.62

The extrapolated percentages from US and Belgium studies indicate that our hospitals are somewhat lagging behind in reduction of the co-prescription.

Data from the present study reveal a substantial percent of patients who are non-adherent to the tamoxifen therapy. This presents an issue because non-adherence to tamoxifen therapy has been linked to poor survivability and increase in all-cause mortality (Mc Cowan et al., 2008; Moon et al., 2017) and lower breast cancer event-free time (Dezentje et al., 2010). The study has a local significance because of several reasons. Firstly, it is the first study in Riyadh, Saudi Arabia to document such prevalence. Secondly, all patients who used tamoxifen were included from two tertiary hospitals in the capital. Thirdly, the study looked at all CYP2D6 without restricting to certain group such as SSRIs or antidepressants in general which was done by other studies. In addition, the study examined adherence because it is a reliable method of assessing adherence (Anghel et al., 2019). Failing to present to fill prescription is more indicative of non-adherence that other methods of assessment such as patient diaries and bill count.

This study has few limitations. At first, not all tamoxifen users in Saudi Arabia were included. However, obtaining these data would be time and resource consuming and thus a sample of two hospitals was thought to represent the population but still there maybe space for studies that include more hospitals in the future. Another limitation might be the short time period set by us especially when compared with other studies. Other limitations include missing of patients' diagnosis and incompleteness of data by physicians. Nonetheless, our objective was not to assess trend as it was for other studies but to assess prevalence, although future studies will be undertaken to document that trend which might be helpful especially for predictive studies. Forthcoming studies are needed to document reasons for non-adherence especially primary non-adherence. Other alternative to CYP2D6 inhibitors such as gabapentin might be incorporated more in the studies to show that they reduce tamoxifen side effects without negating its efficacy. This will increase health care providers' confidence to prescribe the alternatives. Several recommendations could be outlined from the study. Letters could be authorized for organizations such as Saudi FDA to be distributed to prescribers emphasizing this co-prescription percentage. As for primary non adherence, one reason for it might be that many patients come to the capital from remote areas to fill their medications. Policies could be implemented to this subgroup of patients to have more drugs available each fill so number of fills would be reduced and adherence increased.

5. Conclusion

Our observational study on breast cancer patients did not find any link between concomitant CYP2D6 inhibitor use and recurrence for the treatment with adjuvant tamoxifen. However, the prescription of weak inhibitors with tamoxifen increased in the second year as opposed to decrease in the prescription of strong inhibitors. Also we did find a substantial percentage of patients to be non-adherent to tamoxifen therapy.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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