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BRIEF REPORT

Unjustified prescribing of CYP2D6 inhibiting SSRIs in women treated with tamoxifen

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Abstract Tamoxifen is a largely inactive pro-drug, requiring metabolism into its most important metabolite endoxifen. Since the cytochrome P450 (CYP) 2D6 enzyme is primarily involved in this metabolism, genetic polymorphisms of this enzyme, but also drug-induced CYP2D6 inhibition can result in considerably reduced endoxifen formation and as a consequence may affect the efficacy of tamoxifen treatment. Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) have been effectively used for the treatment of depression and hot flashes, both of which occur frequently in tamoxifen-treated women. Due to the drug–drug interaction considerably reduced endoxifen concentrations by inhibition of CYP2D6 will be the result. Evidence of a significant influence of strong CYP2D6-inhibiting drugs on the pharmacokinetics of tamoxifen has resulted in recommendations to avoid potent CYP2D6-inhibiting antidepressants (e.g., paroxetine, fluoxetine) in patients treated with tamoxifen for breast cancer. Nevertheless, dispensing data for tamoxifen and seven regularly used SSRIs/SNRIs in the period between 2005 and 2010, obtained from a large community pharmacy database in the Netherlands (3,000,000 people), show that the potent CYP2D6-inhibiting drug paroxetine remains one of the most frequently used antidepressants in tamoxifen-treated patients. Moreover, trends in the use of SSRIs/SNRIs in the population of all women were similar with trends in women using tamoxifen. Apparently, the recommendations to avoid paroxetine in tamoxifen-treated women have not been implemented into clinical practice. Several reasons may underlie continued use of this drug–drug combination. Contrary to *CYP2D6* polymorphisms, drug-induced CYP2D6 inhibition can easily be avoided, since alternative drugs are available. In clinical practice, one should strive to avoid potent CYP2D6 inhibitors as much as possible in tamoxifen-treated patients to reduce the risk of compromising the efficacy of the hormonal therapy. Co-medication should be reviewed by both physicians and pharmacists and potent CYP2D6 inhibitors ought to be switched to weaker alternatives.

Keywords Tamoxifen · Antidepressants · CYP2D6 inhibitor · Breast cancer

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Tamoxifen and antidepressants

Tamoxifen is an important and effective endocrine therapy in patients with estrogen-receptor positive breast cancer. However, the success story of this old drug is limited by the

fact that a considerable percentage of patients eventually experience a relapse of disease or disease progression [1, 2].

The Achilles' heel of this antiestrogen therapy is that tamoxifen is a largely inactive pro-drug, requiring metabolism into the active metabolites 4-hydroxytamoxifen and in particular endoxifen to reach its effect. This metabolism is catalyzed by the cytochrome P450 (CYP) system, with a crucial role for CYP2D6 [3]. Partly due to the highly polymorphic nature of the *CYP2D6* gene, with more than eighty different alleles known, mainly associated with reduced or absent enzyme activity, the extent of metabolic conversion of tamoxifen into endoxifen varies greatly between patients. This most probably affects the efficacy of tamoxifen treatment [4]. As observed recently, endoxifen possibly needs to exceed a minimum threshold concentration to achieve therapeutic effect [5, 6].

Also drug-induced CYP2D6 inhibition can seriously disrupt the formation of active tamoxifen metabolites and as a consequence may interfere with the efficacy against breast cancer [7]. Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs)—both antidepressant drugs—are frequently co-prescribed in patients on tamoxifen therapy for the treatment of a range of mental disorders. Breast cancer patients commonly suffer from hot flashes as a consequence of breast cancer treatment, including tamoxifen, for which SSRIs and SNRIs may also be used. In addition to clonidine and the anticonvulsant gabapentin, several SSRIs and SNRIs, including paroxetine, fluoxetine, citalopram, and venlafaxine, effectively reduce the incidence and severity of hot flashes [8–10]. Unfortunately, all these antidepressant drugs inhibit CYP2D6 enzyme function, thereby reducing endoxifen plasma concentrations, although the degree of inhibition varies among the different compounds [11–13]. Paroxetine and fluoxetine have been associated with the greatest ability to inhibit CYP2D6 activity and significant, up to 66 % reduced endoxifen plasma concentrations were observed in tamoxifen-treated patients receiving these drugs concomitantly [4, 13]. Co-administration of these CYP2D6 inhibitors seemed to reduce the efficacy of tamoxifen treatment [14]. The effects of CYP2D6 inhibitor use on efficacy of tamoxifen treatment have been examined in subsequent studies. For instance, it was found that women receiving paroxetine concurrently with tamoxifen appeared to have a higher risk of breast cancer mortality, with increases in mortality risk related to the duration of concomitant use [15]. Also, an increased risk of recurrence with the concomitant use of moderate/strong CYP2D6-inhibiting drugs has been reported [16], although this was not found by others [17, 18]. As a safe alternative, antidepressants with limited CYP2D6-inhibiting properties, such as venlafaxine and (es)citalopram, may be used as these drugs lead to less or no interference with tamoxifen metabolism [4, 13].

Trends in the use of antidepressants

Based on the evidence of a clinically relevant influence of strong CYP2D6 inhibitors on tamoxifen metabolism and also the strong biological rationale, caution is warranted for concomitant use of CYP2D6 inhibitors in tamoxifen-treated patients. Combined use of tamoxifen and potent CYP2D6-inhibiting SSRIs should be avoided in patients receiving tamoxifen for breast cancer, which has been recommended in clinical guidelines and incorporated in a changed drug label for tamoxifen [4, 7, 10, 13, 14, 19–21]. Given these recommendations, one would expect to see minimization of the use of these antidepressants among tamoxifen-treated women over the last years. Surprisingly, this is not the case. We have closely monitored dispensing data for tamoxifen and seven commonly used antidepressants, associated with CYP2D6 inhibition, in the period from 2005 to 2010. Dispensing data were derived from a community pharmacy database (PHARMO-Institute for Drug Outcome Research, Utrecht, The Netherlands). This database contains complete drug-dispensing histories from community pharmacies of more than three million people of 48 carefully selected geographic regions (urban and rural) in the Netherlands and forms a representative sample for the Western European society. Patients with all types of health insurance and regardless of prescriber are registered in these community pharmacies. All patients can be followed from the first drug dispensing in a PHARMO community pharmacy until the end of follow-up (loss to follow-up in PHARMO community pharmacy or death) or end of study period (31 December 2010). Data that were available included dispensed drug, coded according to Anatomical Therapeutic Chemical (ATC) Classification, dose regimen, dispensed quantity, date of dispensing, and estimated duration of use.

In the period between 2005 and 2010, dispensing data of $\sim$1.5 million women were available in the community pharmacy database of PHARMO. Tamoxifen use in this population ranged from 3,885 users in 2005 to 3,509 women receiving tamoxifen in 2010. The prevalence of use of the seven antidepressant drugs in the population of women receiving tamoxifen as well as in the population of all women was determined. The number of women receiving tamoxifen as well as an antidepressant drug during the same period was determined per calendar year, defining concomitant users. Duration of (concomitant) use of both drugs was determined using dispensing dates and dispensed quantities. To distinguish between occasional versus regular use of antidepressants during tamoxifen

treatment, regular or long-term use was defined as concomitant use of an antidepressant and tamoxifen for 3 months (≥90 days) or longer. In the population of women using tamoxifen, ~14 % appeared to receive one of the seven antidepressants concurrently (ranging from 11.8 % in 2005 to 14.9 % in 2009). The largest proportion of these women, around 80.9 % (ranging from 78.9 to 82.5 %), received regular antidepressant treatment (concomitant use for at least 90 days). The use of the antidepressants in the population of all women appeared to be about 4.6 % (ranging from 4.3 to 4.9 %). Trends in the use of antidepressants over time in all women were compared with trends in women receiving tamoxifen.

Figure 1 shows that within the population of women receiving tamoxifen, the number of women receiving the strong CYP2D6 inhibitor paroxetine decreased over time, while there was an increase in the use of venlafaxine and (es)citalopram. However, similar trends in the use of these antidepressants were observed in the population of all women (Fig. 2), with a drop in paroxetine use. The proportion of decrease in paroxetine use was comparable in both populations, with a reduction around 30 % (33.7 vs. 28.7 %) in the period from 2005 to 2010. This suggests that the observed changes may have been related to marketing activities or to changes in guidelines for the general population, and not specifically related to new insights in the treatment of hot flashes or depression in tamoxifen-treated patients. In 2010, in this population-based study of ~1.5 million Dutch citizens, no less than 156 out of 3,509 women treated with tamoxifen received paroxetine or fluoxetine concomitantly, while this number should be close to zero.

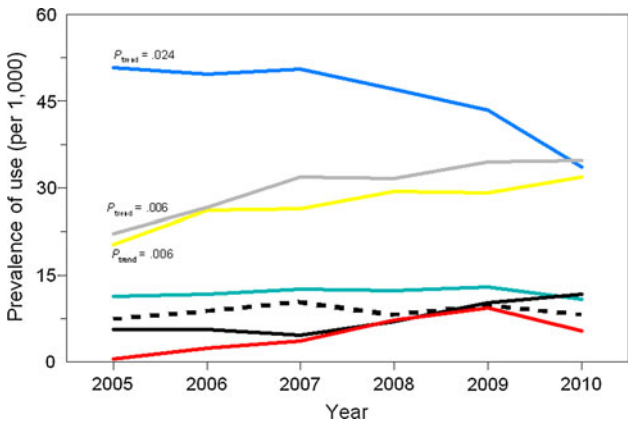

Fig. 1 Prevalence of use of seven commonly used antidepressants, associated with CYP2D6 inhibition, per 1,000 women receiving tamoxifen in the period between 2005 and 2010. The following antidepressants are shown, in the order of their CYP2D6-inhibiting properties, paroxetine (*blue*); fluoxetine (*cyan*); sertraline (*black* (*dashed line*)); fluvoxamine (*black*); citalopram (*yellow*); escitalopram (*red*); and venlafaxine (*gray*). *P* values for trends are shown for paroxetine, citalopram, and venlafaxine

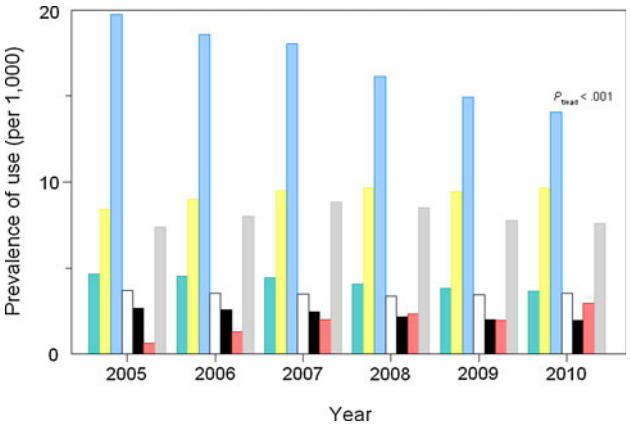

Fig. 2 Prevalence of use of seven commonly used antidepressants, associated with CYP2D6 inhibition, in the population of all women in the period between 2005 and 2010 (PHARMO-dataset). Prevalence of use are shown for paroxetine (*blue*); fluoxetine (*cyan*); sertraline (*white*); fluvoxamine (*black*); citalopram (*yellow*); escitalopram (*red*); and venlafaxine (*gray*). *P* value for trend is shown for paroxetine

Co-prescription of potent CYP2D6-inhibiting antidepressants among tamoxifen users

Despite the recommendations to avoid potent CYP2D6-inhibiting drugs and changes in the drug label for tamoxifen including information on CYP2D6 inhibitor use, complete avoidance of strong CYP2D6-inhibiting antidepressants is far from realized, as we show in the PHARMO database-analysis. Although we did observe a trend towards a decrease in concomitant use of paroxetine and tamoxifen, this highly potent CYP2D6 inhibitor continues to be one of the most frequently used antidepressants in women treated with tamoxifen. Several plausible reasons may contribute to this observation.

First of all, this drug–drug interaction can be easily ignored, since it has no direct adverse consequences, and the antidepressant helps to reduce the severity of hot flashes. In contrast to drug–drug interactions which cause increased exposure of the drug, resulting in an increased risk of developing side effects, drug–drug interactions leading to impaired efficacy of the drug due to reduced bioactivation, as with the pro-drug tamoxifen, appear to be overlooked [22]. The clinical effect of reduced efficacy, in this case a higher risk of breast cancer recurrence, takes some time to occur.

Second, the two drugs are most often prescribed by different physicians. Tamoxifen would be initiated by the oncologist, while paroxetine is most likely started by the general practitioner. Patients may also receive their medication from different pharmacies, for example, a patient may receive one drug from an outpatient pharmacy and the other drug from a community pharmacy [23]. As a result the drug–drug interaction remains unnoticed. In the

Netherlands, pharmacy information systems of outpatient pharmacies and community pharmacies are not coupled to each other. Therefore, both pharmacists and physicians should be extremely alert on identifying co-medication in patients who receive or who will receive tamoxifen treatment. In clinical practice, the use of co-medication, especially antidepressants, should always be inquired with the patient by both healthcare providers.

Third, the combination of drugs is believed to be inevitable by the patient or physician, especially in patients already on paroxetine treatment at the time of starting tamoxifen. Patients are comfortable with the treatment, and discontinuation of the drug may not be preferred. Stopping or switching antidepressant drugs may be rather difficult, as observed in clinical practice. When continuation of therapy with an antidepressant drug is desired, an alternative antidepressant which adequately controls a patient's symptoms is important. Because a discontinuation syndrome is well-known for antidepressants, particularly for paroxetine, antidepressants have to be cross-tapered. For these reasons, it is important to stop or switch antidepressant drugs under careful supervision of an experienced psychiatrist.

Discussion and recommendations

Currently available data regarding the effects of potent CYP2D6-inhibiting drugs on breast cancer recurrence and mortality are conflicting [14–18]. Nevertheless, no information on endoxifen levels was available in these studies. Potential confounding by drug indication may have influenced the results of these studies as patients suffering from depression or tamoxifen-related hot flashes may be less compliant with hormonal therapy. Genotyping for *CYP2D6* was also not performed in most of the studies. Similarly, inconsistent results have been found in studies evaluating the influence of genetic variation in *CYP2D6* on the efficacy of tamoxifen therapy [14, 24–27]. Two large prospective trials, ATAC and BIG 1-98, did not find an association between *CYP2D6* genotype and breast cancer outcome [26, 27], however, the validity of genotype data in these studies has been questioned [28]. Nevertheless, in tamoxifen-treated patients, the importance of endoxifen concentrations is becoming more and more recognized. Concentrations possibly have to be above a minimum level for achieving its protective effect [5]. More evidence which support concentration-dependent effects of endoxifen in women treated with tamoxifen has recently been published. In this study, molecular mechanisms of endoxifen, 4-hydroxytamoxifen, and a pure anti-estrogen were investigated. It was shown that mechanisms of action differed between endoxifen and 4-hydroxytamoxifen. Gene expression profiles of MCF7 cells differed between the substances as well as between different endoxifen concentrations [6]. Therefore, it seems likely that potent CYP2D6-inhibiting drugs affect efficacy of tamoxifen treatment by reducing endoxifen concentrations and should not be used along with tamoxifen to increase the likelihood of receiving optimal benefit from tamoxifen therapy.

In contrast to a diminished CYP2D6 enzyme activity due to genetic polymorphisms, impaired CYP2D6 metabolism by inhibiting co-medication can easily be avoided, especially in case of antidepressants, as there is a broad range of alternatives available when there is a strong indication for these compounds. Despite risks and difficulties associated with switching or stopping antidepressants this should be considered in most women. When non-CYP2D6-inhibiting alternatives are not available or unsuitable for the patient, weak or moderate CYP2D6-inhibiting antidepressants may be prescribed as a "second best" alternative. Venlafaxine and citalopram as well as the s-enantiomer of citalopram, escitalopram, are considered to be safe(r) alternatives for the treatment of depression or hot flashes in tamoxifen-treated patients, as their CYP2D6-inhibiting potential is either mild or absent [10–12]. Only slightly decreased endoxifen concentrations were found in patients receiving weak CYP2D6 inhibitors, including citalopram, compared with patients receiving no CYP2D6-inhibiting drugs. Venlafaxine appeared to have no effect on endoxifen concentrations when used concomitantly with tamoxifen; both in patients carrying two functional *CYP2D6* alleles and in patients with variant alleles [13]. However, an intra-patient comparison has not been performed yet. In a Danish population, no increased breast cancer recurrence rate was observed in tamoxifen-treated patients receiving citalopram or escitalopram concomitantly compared to women taking tamoxifen without this antidepressant [29]. Yet, none of the studies found higher recurrence rates or increased risk of death in patients receiving tamoxifen and venlafaxine at the same time [15, 17, 18].

Moderate inhibitors of CYP2D6, such as sertraline, can decrease endoxifen plasma concentrations, however, not to a similar extent as paroxetine [13]. Nevertheless, current evidence on the clinical effects of the use of weak/moderate CYP2D6 inhibitors in tamoxifen-treated patients is scarce, complicating clinical decision-making whether to use these drugs concurrently with tamoxifen. Recommendations on avoidance of weak/moderate CYP2D6 inhibitors in patients with reduced CYP2D6 activity, according to genotype [10, 19], should be interpreted with caution since low endoxifen concentrations also have been found in patients with two functional alleles [30], making these patients less suitable for receiving CYP2D6-inhibiting drugs as well. The direct impact of various CYP2D6-inhibiting drugs on the pharmacokinetics of tamoxifen in

relation with clinical outcome has to be prospectively evaluated, with inclusion of a patient's *CYP2D6* genotype. Such a trial is currently ongoing at our cancer center, where patients using the combination of tamoxifen and a strong CYP2D6 inhibiting antidepressant are switched to a drug with little or no CYP2D6-inhibiting properties (Dutch trial registry number NTR3125). Following switching, changes in the pharmacokinetics of active tamoxifen metabolites are examined within individual patients. Awaiting these study-results, one should use weak/moderate CYP2D6 inhibitors with caution in patients receiving tamoxifen, especially moderate CYP2D6 inhibitors.

On the other hand, occurrence of side effects (e.g., hot flashes) may result in poorer adherence to tamoxifen, which has been associated with worse treatment outcome [17, 31]. In clinical practice, persistence to adjuvant endocrine therapy was demonstrated to be suboptimal, ranging from only 27 to 69 % [32], with higher discontinuation rates in patients suffering from treatment-related side effects [33]. Effective therapies for the treatment of hot flashes may therefore be essential to solve problems regarding adherence. In addition, depressive disorders may also negatively affect adherence. The use of antidepressants which have been shown to be effective in the treatment of depressive disorder or alleviation of hot flashes, but possess weak or moderate CYP2D6-inhibiting properties, may therefore be advocated (i.e., venlafaxine, citalopram).

Besides antidepressants, clonidine and gabapentin show benefit in controlling hot flashes and may safely be used in combination with tamoxifen, regarding their pharmacokinetic interaction potential. Nevertheless, disadvantages of these drugs include the occurrence of side effects (e.g., sleep disturbances) in case of clonidine and frequent administration when gabapentin is used, as only a high dose (900 mg/day) appeared to be effective [8, 34, 35]. In general, when antidepressants or other drugs are used for the treatment of hot flashes, the benefit of the drug should outweigh possible negative effects.

In post-menopausal women, necessitating the use of a potent CYP2D6-inhibiting drug, tamoxifen therapy could be replaced with an aromatase inhibitor, however, this should be carefully considered by the medical oncologist, taking into account the tolerability of this endocrine treatment by the patient.

The problem with tamoxifen is, however, more complicated. Even if all tamoxifen-treated patients would stop using strong CYP2D6 inhibitors, this does not imply that the problem is solved. In addition to adherence and genetic polymorphisms of *CYP2D6*, which may have a significant effect on the pharmacokinetics of tamoxifen [13], other drug-metabolizing enzymes and drugs which are able to modulate these enzymes may also affect tamoxifen metabolism [36]. This should be taken into account too. Moreover, impaired metabolism may partly explain variability in response to tamoxifen, however, other mechanisms (e.g., alterations in estrogen receptor expression and function) also underlie tamoxifen resistance [37].

There are some limitations of this study. First, only drug-dispensing data derived from a single community pharmacy database of PHARMO was available, with no validation by other community databases. No demographic or pathological characteristics of the patients were available, also lacking diagnoses for breast cancer. In addition, we did not have information on indication of antidepressant treatment (e.g., depression, hot flashes), co-morbidity, and concomitant use of drugs (other than antidepressants and tamoxifen), factors that might have influenced the selection for a particular (potent CYP2D6-inhibiting) antidepressant drug, which is another important limitation of the study.

Conclusion

In conclusion, despite the strong biological rationale and recommendations to avoid potent CYP2D6-inhibiting co-medication in tamoxifen-treated patients, paroxetine is still frequently prescribed concurrently with tamoxifen, which is undesirable in most cases regarding efficacy of tamoxifen treatment. Further steps should be taken to avoid the concomitant use of these drugs as much as possible to increase the chance of effective hormonal therapy. Pharmacists and physicians should be alert in reviewing co-medication in patients receiving tamoxifen. It is advised that strong CYP2D6 inhibitors are switched to little or no CYP2D6-inhibiting alternatives, whenever possible, and this should be supervised by an experienced psychiatrist. Studies prospectively examining the precise impact of various CYP2D6-inhibiting antidepressants on the pharmacokinetics of tamoxifen in individual patients and in relation with clinical outcome are strongly required.

Conflict of interest The authors declare that they have no conflict of interest.

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