Tamoxifen and SSRI or SNRI antidepressants – is there an interaction?

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Background
The selective oestrogen receptor modulator tamoxifen has been used to treat hormone receptor positive breast cancer in the adjuvant setting for over three decades, where it has been shown to reduce annual breast cancer mortality rate by a third and five-year recurrence by a half [1,2]. Depression and anxiety are common co-morbidities with breast cancer. Estimates suggest 20-30% of patients taking tamoxifen are co-prescribed anti-depressants either for psychiatric reasons, or off-label for vasomotor symptoms [1].

Tamoxifen is a prodrug that is extensively metabolised to more potent active metabolites by cytochrome P450 isoenzymes (CYP450) in the liver [3,4]. Inhibition of these enzymes by certain antidepressants potentially prevents formation of the active compounds, therefore negating clinical effect [3,4].

This Medicines Q&A reviews the evidence for an interaction between tamoxifen and selective serotonin reuptake inhibitors (SSRIs)/serotonin noradrenaline reuptake inhibitors (SNRIs) resulting in reduced tamoxifen efficacy.

Answer

Metabolism of tamoxifen
Formation of primary metabolites is catalysed by CYP2D6, with a much smaller contribution from the CYP3A family. Active metabolites include 4-hydroxy-N-desmethytlamoxifen (endoxifen) and 4-hydroxytamoxifen, both of which are 100-fold more potent anti-estrogens than the parent compound. Serum concentrations of endoxifen are 6-10 times higher than 4-hydroxytamoxifen, therefore it is regarded as the more clinically important metabolite for tamoxifen activity [1,4].

CYP450 iso-enzymes are highly subject to genetic polymorphism, and an individual's capacity to metabolise tamoxifen varies according to their CYP2D6 genotype. Approximately 100 allelic variants of CYP2D6 have been identified, presenting as four phenotypes within the population [5,6,7]:

- poor metabolisers (PM) have two non-functional CYP2D6 alleles and so no CYP2D6 activity,
- intermediate metabolisers (IM) have one functional and one deficient allele resulting in reduced CYP2D6 activity,
- extensive metabolisers (EM) have two functional alleles therefore normal CYP2D6 activity,
- ultra-rapid metabolisers (UM) have multiple functional alleles, causing excess CYP2D6 activity.

Association between CYP2D6 status and clinical outcomes with tamoxifen is controversial, and trial results are inconsistent. One review concluded that whilst CYP2D6 activity does clearly affect endoxifen levels, it is difficult to prove this translates to reduced tamoxifen efficacy; relevant studies are of differing design, methodological quality and statistical power, making it difficult to combine them to enable clinically meaningful conclusions to be drawn [8]. However, most recently published data from a prospective study (n=667) found no association between endoxifen concentrations or CYP2D6 genotypes and clinical outcome in patients with early-stage breast cancer receiving adjuvant tamoxifen [9].

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SSRIs/SNRIs and inhibition of CYP2D6
Different SSRIs and SNRIs inhibit CYP2D6 to varying degrees [10-20].

Of the SSRIs, paroxetine is a potent inhibitor and fluoxetine a moderate-to-potent inhibitor of CYP2D6 [10-14]. Citalopram, escitalopram and sertraline are weak inhibitors of CYP2D6, and fluvoxamine is a moderate inhibitor. With regard to SNRIs, duloxetine is a moderate inhibitor whereas venlafaxine is a weak inhibitor [12-18].

Evidence for a clinically relevant interaction between tamoxifen and SSRIs/SNRIs

SSRIs
Plasma endoxifen levels have been reported to be as much as 66% lower in patients treated with tamoxifen and concomitant paroxetine or fluoxetine than in patients treated with tamoxifen alone, essentially converting phenotypically IM or EM individuals to PMs [14,21].

A small (n=10) prospective pharmacokinetic study examined the effect of switching patients treated for depression or anxiety with a potent CYP2D6 inhibitor (paroxetine (n=8) or fluoxetine (n=2)) to a weak inhibitor (escitalopram) on levels of tamoxifen and its metabolites. Nine were switched to escitalopram, one was accidentally given citalopram. Endoxifen concentration was 3-fold higher with tamoxifen/escitalopram or citalopram, than tamoxifen/fluoxetine or tamoxifen/paroxetine [22].

A 2014 meta-analysis pooled data from twelve epidemiological studies investigating the effect of concomitant SSRIs and tamoxifen on breast cancer recurrence. Summary effect estimate of breast cancer recurrence with tamoxifen and concomitant potent or weak CYP2D6-inhibiting SSRIs was 1.03 [95% CI 0.86 to 1.23] and 1.05 [0.91 to 1.22], respectively. Overall, the data did not suggest that taking either potent or weak CYP2D6-inhibiting SSRIs concurrently with tamoxifen increased risk of relapse; effect of both drug and/or gene-induced inhibition of CYP2D6 is likely to be small, or at most moderate, in individuals with a PM phenotype [14].

A study of 16,887 tamoxifen-treated breast cancer survivors followed for a maximum of 14 years found no statistically increased risk of recurrence associated with concomitant use of antidepressants (paroxetine, fluoxetine, other SSRIs, tricyclics and other classes) with tamoxifen [23].

A population-based cohort study (n=14,532) aimed to compare the difference in mortality between women prescribed tamoxifen with an SSRI that are potent inhibitors of CYP2D6 (fluoxetine or paroxetine) versus women prescribed tamoxifen with other SSRIs (citalopram, escitalopram, fluvoxamine or sertraline); the authors examined data from five US health insurance databases covering an 18-year period. The pooled hazard ratio for death for the potent inhibitors (58.6/1,000 person-years) compared with other SSRIs (57.9/1,000 person-years) was 0.96 [95% CI 0.88 to 1.06]. The authors concluded that SSRIs considered potent inhibitors of CYP2D6 didn’t increase the risk of death from all causes, when compared to other SSRIs [24]. However, an accompanying editorial considers that this study was too short and measured the wrong outcome. In the author’s opinion, it is premature to dismiss an interaction between tamoxifen and SSRIs because of the clinical consequences of an interaction, the plausible mechanism, inconsistent study results, and the challenge of study design in this field. He suggests that weaker inhibitors (i.e. citalopram, escitalopram, sertraline or the SNRI venlafaxine) should be prescribed in preference to more potent inhibitors (i.e. fluoxetine and paroxetine and the SNRI duloxetine) in patients taking concomitant tamoxifen [25].

SNRIs
Mean plasma endoxifen levels were not significantly affected by venlafaxine (n=6) in one study [26]. Another reported mean plasma endoxifen concentration was slightly reduced in patients taking tamoxifen plus venlafaxine, and substantially reduced in those taking tamoxifen plus paroxetine [27]. However, more recent data showed venlafaxine reduced endoxifen levels by 23% [p=0.004] in a
patient population predominantly comprised of UM and EM phenotypes (n=20). The authors state that whilst levels of endoxifen were reduced by venlafaxine, the optimal level of endoxifen for prevention of recurrence remains to be determined [28].

No direct studies involving tamoxifen and the SNRI duloxetine were identified, but as a moderate CYP2D6 inhibitor, theoretically it is expected that lower levels of endoxifen would be produced [1,13].

**Guidance**

The MHRA, NICE Clinical Knowledge Summaries and the manufacturer of tamoxifen all recommend that the potent CYP2D6 inhibitors fluoxetine and paroxetine should not be co-prescribed with tamoxifen [29-31]. Weak inhibitors such as sertraline, citalopram, escitalopram or venlafaxine are more suitable for prescribing in this patient population [25].

Routine pharmacogenetic testing in clinical practice for CYP2D6 alleles prior to initiation of tamoxifen is not currently recommended due to uncertainty regarding type and quantity of alleles to test for, a lack of clinical data and undetermined implementation costs [29,32].

For patients currently taking tamoxifen with an antidepressant considered a potent or moderate CYP2D6 inhibitor (paroxetine, fluoxetine, fluvoxamine, duloxetine) who wish to switch to an antidepressant that is a weak CYP2D6 inhibitor (citalopram, escitalopram, sertraline), advice can be found in the UKMi Q&A 150.5 “How do you switch between tricyclic, SSRI and related antidepressants?”

**Summary**

- Tamoxifen is extensively metabolised via cytochrome P450 2D6 (CYP2D6) to active metabolites, the most significant of which is endoxifen.
- CYP2D6 is highly polymorphic, therefore capacity to metabolise tamoxifen varies according to individual CYP2D6 genotype.
- Different SSRIs/SNRIs inhibit the action of CYP2D6 to varying degrees.
- Epidemiological data are conflicting and inconclusive with regard to the interaction between tamoxifen and SSRIs or SNRIs.
- As the mechanism of effect is biologically plausible, caution is advised when prescribing antidepressants that are potent or moderate inhibitors of CYP2D6.
- Paroxetine is a potent CYP2D6 inhibitor, therefore co-prescribing with tamoxifen is not recommended. Fluoxetine is a moderate-to-potent inhibitor, and fluvoxamine and duloxetine are moderate inhibitors.
- Preference should be given to SSRIs/SNRIs with weak inhibitory effects on CYP2D6, such as citalopram, escitalopram, sertraline and venlafaxine.
- Routine pharmacogenetic testing in clinical practice for CYP2D6 alleles prior to starting tamoxifen is not currently recommended.

**Limitations**

The clinical significance of potential drug interactions between tamoxifen and SSRIs/SNRIs are challenging to study; further data are needed before definitive recommendations can be made.

**References**


Available through Specialist Pharmacy Service at www.sps.nhs.uk


31. Wockhardt UK Ltd. Summary of product characteristics - tamoxifen 20mg film-coated tablets. Updated August 2018 [cited 7/12/18]. Available at: www.medicines.org.uk

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