MHRA UK PUBLIC ASSESSMENT REPORT

Tamoxifen: reduced effectiveness when used with CYP2D6 inhibitors

September 2011

PLAIN-LANGUAGE SUMMARY

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses the evidence that the effectiveness of tamoxifen in treating breast cancer may be reduced by drugs that inhibit a protein in the body called CYP2D6.

Tamoxifen is a widely used and effective treatment for breast cancer. In order to work, tamoxifen is metabolised[a] in the body by an enzyme[b] called cytochrome P450 isoenzyme 2D6 (CYP2D6). The substances produced by the metabolism of tamoxifen are the active compounds that treat the cancer.

Some medicines block the function of CYP2D6, and consequently may interfere with the cancer-fighting actions of tamoxifen if they are given around the same time. A group of antidepressant medicines called selective serotonin reuptake inhibitors (SSRIs) are particularly relevant for this issue, as they inhibit CYP2D6 to varying degrees, and may be commonly prescribed to treat depression in women with breast cancer. They are also used to treat hot flushes[c], an adverse drug reaction (side effect) that may occur with tamoxifen use, although this is not a licensed use for these medicines.

CYP2D6 function can also naturally vary between individuals – this variation is inherited (ie, genetic) and referred to as 'CYP2D6 genetic polymorphism'. Some individuals are categorised as 'poor metabolisers', and demonstrate little or no CYP2D6 activity; potentially, the effectiveness of tamoxifen in treating breast cancer may be reduced in these individuals, regardless of any other medicines they may be taking.

Therefore, as CYP2D6 inhibition may have serious consequences for clinical outcomes in patients treated with tamoxifen for breast cancer, the scientific and clinical data on this issue have been reviewed both in the UK and in Europe. This report summarises the available evidence on whether clinical outcomes in tamoxifen-treated cases of breast cancer are affected by:

- Drugs that inhibit CYP2D6, such as SSRIs
- CYP2D6 genetic polymorphism

Results

Effect of CYP2D6 inhibitors on clinical outcomes with tamoxifen

A published study has shown that in a population of women treated with tamoxifen for breast cancer, the risk of death from breast cancer increased in women who, at the

[a] Broken down in the body to produce other substances
[b] Proteins produced by cells in the body that metabolise substances and help specific biological reactions to occur
[c] Feeling of intense heat with sweating and rapid heartbeat

same time, were also receiving paroxetine, an SSRI antidepressant and potent CYP2D6 inhibitor.

A second study found no evidence that the use of CYP2D6 inhibitors reduced the effectiveness of tamoxifen; however there is still a strong biological rationale supporting this interaction. Therefore it is recommended that the use of any strong CYP2D6 inhibitor should be avoided wherever possible in patients taking tamoxifen.

Effect of CYP2D6 genetic polymorphism on tamoxifen effectiveness

There are currently 19 published clinical studies which have evaluated the association between *CYP2D6* polymorphism (ie. individuals who vary in their natural level of CYP2D6 function) and clinical outcomes in patients treated with tamoxifen for breast cancer. Many of these studies had limitations and the evidence for such an association is mixed and inconclusive. Patients treated with tamoxifen for breast cancer who have naturally reduced levels of CYP2D6 activity do not, on the whole, demonstrate worse clinical outcomes than patients treated with tamoxifen who have normal CYP2D6 activity.

Therefore, although *CYP2D6* genetic polymorphism may be associated with variability in treatment outcomes with tamoxifen, there is currently no recommendation for genetic testing to determine CYP2D6 status in patients before beginning tamoxifen treatment.

Conclusions

- Medicines that inhibit CYP2D6 enzyme activity can interfere with the actions of tamoxifen and reduce its effectiveness in treating breast cancer

- It is therefore recommended that the use of medicines that are known to be strong or potent CYP2D6 inhibitors should be avoided in patients taking tamoxifen. Examples of such medicines are:

  Paroxetine (brand name Seroxat)[a]

  Fluoxetine (Prozac)[b]

  Buproprion (Zyban)[c]

  Quinidine[d] (no brand name)

  Cinacalcet (Mimpara)[e]

- There is currently no recommendation for *CYP2D6* gene testing in patients before starting tamoxifen treatment.

[a] an SSRI antidepressant
[b] an SSRI antidepressant
[c] a medicine to treat depression and aid smoking cessation
[d] a treatment for arrhythmia (an abnormal or irregular heartbeat)
[e] a treatment for complications caused by end-stage renal (kidney) disease

The above information and advice have been communicated in an article in Drug Safety Update, the monthly MHRA publication containing the latest information and advice on medicines and vaccines safety.

1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. The following report discusses the evidence on whether the use of CYP2D6 inhibitors or CYP2D6 genetic polymorphisms can cause a clinically relevant reduction in the efficacy of tamoxifen used to treat breast cancer.

2. BACKGROUND

Tamoxifen is a selective oestrogen receptor modulator widely used in the management of breast cancer. It works by attaching to oestrogen receptors in breast cells and blocking the effects of oestrogen in this area. This in turn inhibits the growth of oestrogen-dependent/sensitive breast cancer cells. Tamoxifen is generally well tolerated; however, up to 80% of women who take tamoxifen experience hot flushes (also known as hot flashes), and up to 45% grade them as severe[1]. The hot flushes experienced with tamoxifen are associated with the lowered oestrogen levels resulting from treatment.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are increasingly used to treat tamoxifen-related hot flushes (although this is not a licensed use for these medicines)[a]. In addition, the prevalence of depression in women with breast cancer is roughly twice that of the general female population,[2] which may also be reflected by a high use of antidepressants such as SSRIs in this population.

Several studies have demonstrated that most of the active, antiproliferative effects of tamoxifen on breast cancer are mediated by its metabolites 4- hydroxytamoxifen and endoxifen[3-9]. Endoxifen is mainly formed via the actions of the polymorphic cytochrome P450 isoenzyme 2D6 (CYP2D6), of which there are 100 genetic variants[10].

Moreover, several medicines, including some SSRIs such as paroxetine and fluoxetine, are potent inhibitors of CYP2D6. In addition, genetic polymorphism of the *CYP2D6* allele exists in the population, with four distinct phenotype categories related to CYP2D6 activity identified: extensive metabolisers (normal activity), intermediate (reduced activity), poor (no activity) and ultrarapid (high activity). The consequences of reduced CYP2D6 activity, due to either natural causes or interaction with concomitant medication, may be serious particularly for the effectiveness of medicines such as tamoxifen which depends on this enzyme for activation. It is important that both healthcare professionals and patients should be aware of such potential interactions, particularly as some CYP2D6 inhibitors, such as SSRIs, are widely used in patients receiving tamoxifen. After a European

[a] See product information for tamoxifen in the electronic medicines compendium for more details (www.medicines.org.uk/emc)

assessment of evidence in 2008, the following warnings were added to the Summary of Product Characteristics[a] (SPC) for the SSRI paroxetine (brand name Seroxat):

Seroxat SPC:

- Section 4.4 (special warnings and precautions for use): "paroxetine may lead to reduced efficacy of tamoxifen (see section 4.5). It is recommended that prescribers consider using alternative antidepressant with minimal CYP2D6 activity."

- Section 4.5 (interaction with other medicinal products and other forms of interaction): "tamoxifen is a prodrug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite and hence reduced efficacy of tamoxifen, especially in extensive metabolisers. It is recommended that prescribers consider using an alternative antidepressant with minimal CYP2D6 activity."

In addition, the SPC for tamoxifen contains the following warning on interactions with CYP2D6 inhibitors: "Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen), has been reported in the literature".

It is important to continually monitor any factors that may affect the clinical effectiveness of tamoxifen for breast cancer. Therefore, scientific and clinical data on the effects of known CYP2D6 inhibitors, and the potential effects of *CYP2D6* genetic variation, on clinical responses to tamoxifen in patients with breast cancer have recently been assessed, both in Europe by the Pharmacogenomics Working Party (an EU Expert Working Group) and in the UK by the MHRA and its independent expert advisory committees[b]. The results and conclusions are discussed below.

[a] Product information for health professionals. See electronic medicines compendium (eMC) website for more details (www.medicines.org.uk/emc)

[b] See http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines/ExpertAdvisoryGroups/index.htm for more details

3. DATA CONSIDERED

The following table summarises the data from a review of worldwide studies which examined the effects of genetic polymorphisms of the CYP2D6 enzyme on the clinical effects of tamoxifen[11]. Two more recent studies which examined a possible link between CYP2D6 genotypes and tamoxifen outcomes, as well as two studies which looked at the clinical impact of the interaction between tamoxifen and CYP2D6 inhibitors were assessed after this review was published; these are discussed below in a separate section (3.1).

Table 1. Summary of clinical studies that have evaluated the association between *CYP2D6* genotype and tamoxifen-related clinical outcomes in Caucasian[a] breast cancer patients. [b]

Author	Patients	*CYP2D6* alleles typed	Median follow-up (years)	CYP2D6 inhibitors in PM definition	Comparison	Main Results
Goetz et al. 2005[12]	N=190 ER+ve Postmeno-pausal TAM only	*4, *6	11.4	No	PM vs. EM + hetEM	DFS HR, 1.86; *P* = 0.089 RFS HR, 1.85; *P*= 0.176 OS HR, 1.12; *P*= 0.780
Goetz et al. 2007[13]	N=190 ER+ve Postmeno-pausal TAM only	*4, *6	11.4	Yes	PM vs. EM + hetEM	RFS HR, 1.74; *P* = 0.02 TTBR HR, 1.91; *P*=0.034 DFS HR, 1.60; *P*= 0.027 OS HR,

[a] Studies on Caucasian populations were focussed on as there is more available data for assessment in this population

[b] Table adapted from Ferraldeschi F, Newman W. The impact of CYP2D6 genotyping on tamoxifen treatment. Pharmaceuticals 2010; 3: 1122 - 1138

						1.34; *P*= 0.223
Goetz et al. 2008[14]	N=210 ER+ve Postmeno-pausal TAM only	*10, *17, *41 *3, *4, *6	14.5	Yes	PM vs. EM	TTR HR 4.0, *P*=0.001 DFS HR 2.0, *P*=0.02
Schroth et al. 2007[15]	N=206 ER+ve TAM only	*4, *5, *10, *41	5.9	No	hetEM + IM+PM vs EM	RFT HR 2.24; *P* = 0.02 EFS HR 1.89; *P* = 0.02
Newman et al. 2008[16]	N=115 Familial breast cancer ER+ and -ve Adj TAM Some received CT	*3,*4,*5,*41	10	Yes	PM vs EM+ hetEM	TTR HR, 2.1; *P* = 0.14 OS HR, 2.5; *P* = 0.17 *BRCA2*patients DFS HR, 3.8; *P* = 0.083 OS HR, 9.7; *P* = 0.008
Bijl et al. 2009[17]	N=85 Adj TAM	*4	Not available	Yes	PM vs EM	BCM HR, 4.0; *P* = 0.025
Gonzalez-Santiago et al. 2008[18]*	N=84 Adj TAM	*4	5.5	No	hetEM + PM vs EM	RFS HR, 2.82; *P* = 0.05

Ramon et al. 2009[19]	N=91 ER+ve Adj TAM Some received CT	Amplichip[a] 33 alleles	9	No	PM vs hetEM + IM+PM	DFS HR not available, P = 0.016
Nowell et al. 2005[20]	N=162 Adj TAM Some received CT	*3,*4,*6	Not available	No	PM + hetEM vs EM	OS HR, 0.77; P = 0.51 PFS HR, 0.67; P= 0.19
Wegman et al. 2005[21]	N=226 ER + and -ve Some received CT Some received TAM	*4	10.7	No	Not applicable	Carriers of the *CYP2D6 *4* allele demonstrated a decreased risk of recurrence when treated with TAM (relative risk, 0.28; *P* =0.0089)
Wegman et al. 2007[22]	N=677 ER+ve Postmenopausal Some received CT, different dose-different duration of	*4	7.3	No	PM vs. EM + hetEM	RFS HR, <1; P = 0.055

[a] A clinical test for specific gene types

	TAM					
Schroth et al. 2009[23]	N=1325 TAM only	*3,*4,*5,*10*41	6.3	No	hetEM+IM +PM vs EM	EFS HR, 1.33; *P*=0.01 DFS HR, 1.29; *P*=0.02
Thompson et al. 2009*[24]	N=618 ER+ve Adj TAM Some received CT	Amplichip 33 alleles	5.6	No	hetEM+ IM +PM vs EM	RFS HR 1.52, *P*=0.06 Postmenopausal, TAM only patients: RFS HR, 1.96; *P*=0.036

*=abstract only. N=number of patients; TAM=tamoxifen; CYP2D6=cytochrome P450 2D6; PM=poor metaboliser (CYP2D6 genetic variant); CT=chemotherapy; BCS=breast cancer survival; DFS=disease-free survival; BCM=breast cancer mortality; EFS=event-free survival; DRFS=distant recurrence-free survival; ER-+ve=oestrogen±progesterone-positive tumour; ER-ve=oestrogen- ± progesterone-negative tumour=hetEM – individuals with one normal *CYP2D6* allele and one null activity allele have been classified in some studies as a separate phenotype group; PFS=progression-free survival; RFS=recurrence-free survival; RFS=relapse-free survival; TTBR=time to breast cancer recurrence, TTR=time to recurrence; RFT=relapse-free time, EFS=event-free survival: OS=overall survival; HR=adjusted Hazard Ratio; *P*=P-value

Many studies had limitations such as that by Scroth et al, 2009[22]. The limitations included a lack of information about co-medications (eg, use of CYP2D6 inhibitors), and discrepancies in the results of DNA testing due to where the sample was taken from. The data from these studies, as well as the results from four other studies by Lash et al, 2009[25], Kiyotani et al, 2010[26] Bonanni et al, 2006[27] and Abraham et al, 2010[28] suggest that the evidence linking various poor metaboliser genotypes and tamoxifen treatment outcomes is mixed and inconclusive. There appears to be no robust association between genotype and the effectiveness of tamoxifen or survival

time after treatment, and no strong basis to recommend genetic testing before treatment with tamoxifen.

3.1 Recent data in detail

CYP2D6 polymorphism and tamoxifen treatment outcomes

The most recent data on the issue of a possible correlation between CYP2D6 metaboliser status and variations in tamoxifen treatment outcomes are from two ongoing clinical studies, ATAC and BIG 1-98. The data were presented in abstract form at the San Antonio Breast Cancer Symposium in December 2010.

The first abstract by Rae et al, 2010[29] presented data on *CYP2D6* genotype and rates of breast cancer recurrence obtained from over 1000 patients in the ATAC clinical trial (a prospective, randomised, double-blind, placebo-controlled trial which compared the adjuvant use of anastrozole versus tamoxifen treatment for breast cancer over 5 years, with a 10-year follow-up). The authors of this abstract found no association between *CYP2D6* genotype and rates of breast-cancer recurrence in tamoxifen-treated patients, and concluded that these data do not support the hypothesis that patients with decreased CYP2D6 enzyme activity receive less benefit from tamoxifen therapy compared to those with normal CYP2D6 activity.

The second abstract by Leyland et al, 2010[30] presented data on the possible correlation between *CYP2D6* genetic variation and breast-cancer-free interval and onset of hot flushes or night sweats, in 2000 patients from the BIG 1-98 clinical trial (a double-blind, randomised trial which compared 5 years of treatment with either letrozole or tamoxifen in postmenopausal women with breast cancer). The authors of this abstract found that *CYP2D6* genotypes of reduced activity (poor metabolisers and intermediate metabolisers) were not associated with worse disease control or reduced hot flushes, and concluded that *CYP2D6* pharmacogenetic testing is not justified to determine whether to give tamoxifen to treat breast cancer.

The results from these two latest studies support the findings from previous studies that there is no basis to recommend genotyping of patients before starting treatment with tamoxifen.

Tamoxifen treatment outcomes with concomitant use of CYP2D6 inhibitors

A study by Kelly et al, 2010[31] looked at the risk of death from breast cancer after completion of tamoxifen treatment, in women age 66 years or older who had overlapping treatment with a single SSRI.

Of 2430 women treated with tamoxifen and a single SSRI, 374 (15.4%) died of breast cancer during follow-up (mean follow-up: 2.38 years, standard deviation [SD]: 2.59).

After adjustment for age, duration of tamoxifen treatment, and other potential confounders, the data showed that increases in the proportion of time on tamoxifen with overlapping use of the SSRI paroxetine (an irreversible inhibitor of CYP2D6) were associated with significant proportional increase in the risk of death from breast cancer (see Table 2).

Table 2. Paroxetine exposure and risk of death from breast cancer in women receiving paroxetine

Proportion of time on tamoxifen overlapped with paroxetine use (%)	Increase in risk of death from breast cancer (%)	Adjusted HR (95% CI)*
25	24 (p<0·05)	1·24 (1·08–1·42)
50	54 (p<0·05)	1·54 (1·17–2·03)
75	91 (p<0·05)	1·91 (1·26–2·89)

HR=hazard ratio; CI=confidence interval
*Adjusted for age, duration of tamoxifen treatment, timing of tamoxifen in relation to breast cancer diagnosis, socioeconomic status, comorbidity, and receipt of other CYP2D6-inhibiting drugs

By contrast, no such risk was seen with other antidepressants (for 75% increase in time taking the following SSRIs with tamoxifen: fluoxetine: HR 0.91 [95% CI 0.55–1.51]; sertraline: 0.99 [0.67–1.47]; fluvoxamine: 0.94 [0.53–1.66]; citalopram: 1.33 [0.56–3.17]). The authors concluded that insufficient study size was the reason the mortality results did not reach significance with SSRIs other than paroxetine. There was a trend towards reduced breast cancer mortality among patients exposed to venlafaxine which has minimal CYP2D6 inhibition and is commonly used off-label to treat hot flushes[32].

It is estimated that if patients used paroxetine for 41% of the duration of their tamoxifen treatment (the median overlap time in the sample) this would result in one additional breast cancer death within five years of cessation of tamoxifen for every 19.7 (95% CI 12.5–46.3) patients treated; the risk with more extensive overlap would be expected to be greater.
This study did not provide essential detail on the genotype of the women studied or information on their stage of breast cancer. However, the evidence was sufficient for the authors to conclude that paroxetine use during tamoxifen treatment is associated with an increased risk of death from breast cancer. This supports the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer.

A more-recent study by Dezentje et al, 2010[33] looked at concomitant CYP2D6 inhibitor use with tamoxifen treatment for breast cancer in 1,962 patients, with regard to the measure of breast cancer event-free time. Data were obtained from pharmacy and pathology databases.

Although this study found no evidence for decreased efficacy of tamoxifen when co-administered with CYP2D6 inhibitors, there is still a strong biological rationale and large weight of evidence supporting this interaction. Therefore it is recommended that concomitant use of CYP2D6 inhibitors should be avoided whenever possible in patients taking tamoxifen.

4. DISCUSSION AND RECOMMENDATIONS.

There is growing evidence that drugs that strongly inhibit the enzyme CYP2D6, including some SSRIs such as paroxetine, may interact with tamoxifen resulting in a poorer clinical outcome for women taking tamoxifen for breast-cancer treatment.

After consideration of current available data, the European Expert Working Group and MHRA concluded that there is sufficient evidence to suggest a strong association between reduced enzyme activity of CYP2D6 and the risk of lowered tamoxifen response. Although the study by Kelly et al, 2010[31] has important limitations, it adds to the evidence in favour of a clinical impact for interactions between CYP2D6 inhibitors and tamoxifen.

The evidence for an association between *CYP2D6* genetic polymorphism and clinical outcome in patients treated with tamoxifen is mixed and inconclusive. Patients treated with tamoxifen for breast cancer who have naturally reduced levels of CYP2D6 activity do not, on the whole, demonstrate worse clinical outcomes than patients treated with tamoxifen who have normal CYP2D6 activity.

On the basis of the evidence in this report and the above conclusions, the following recommendations have been made to healthcare professionals:

- Concomitant use of medicines that are potent inhibitors of the CYP2D6 enzyme should be avoided whenever possible in patients treated with tamoxifen for breast cancer. Examples of such drugs include:
    - Paroxetine
    - Fluoxetine
    - Bupropion
    - Quinidine
    - Cinacalcet
- Current data for the effect of genetic polymorphisms are insufficient to support recommending genotyping of patients.

This information was included in an article in the November 2010 issue of Drug Safety Update, the monthly MHRA publication containing the latest information and advice on medicines and vaccines safety.

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6. GLOSSARY

4-hydroxytamoxifen
An active **metabolite** formed from the breakdown of **tamoxifen**

Allele
One member of a pair of genes (or segments of DNA) occupying a specific site on a chromosome, that is responsible for a particular physical characteristic or trait of the body

Anastrozole
An **aromatase inhibitor** given to treat breast cancer

Aromatase
An **enzyme** that converts **testosterone** to **oestrogen**

Aromatase inhibitor
Drugs that inhibit the action of **aromatase**, and are used to treat advanced **oestrogen**-dependent breast cancer in women who have gone through the menopause

Buproprion
An antidepressant drug and smoking-cessation aid

Chemotherapy
The prevention or treatment of diseases such as cancer, using chemical substances

Cinacalcet
A treatment for complications caused by end-stage kidney disease

Citalopram
An antidepressant medicine belonging to the **SSRI** drug class

Concomitant medication
Two or more medicines given in the same period

Confound/confounding factors
Where the presence of one **risk factor** changes the effects that another risk factor has on the development of a medical condition; this can affect the results of a study

CYP2D6
A protein in the **Cytochrome P450 isoenzyme 2D6** family

Cytochrome P450 isoenzyme 2D6
A family of proteins which break down many substances in the body

Efficacy
The effectiveness of a drug measured under laboratory conditions or in clinical trials

Endoxifen
An active **metabolite** formed from the breakdown of **tamoxifen**

Enzyme

A protein produced by cells in the body that helps specific biological reactions to occur

Fluoxetine
An antidepressant medicine belonging to the **SSRI** drug class

Fluvoxamine
An antidepressant medicine belonging to the **SSRI** drug class

Genetic polymorphism
Differences in DNA between individuals which can result in naturally different forms, eg, blood group types, or different activity levels of enzymes such as CYP2D6

Hazard ratio
A measure of risk of an event occurring. Hazard ratios with a value greater than 1 suggest increased risk; those equal to 1 suggest equal risk; and those with a value less than 1 suggest decreased risk. The values are usually accompanied by a 95% confidence interval (CI), which indicates there is a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is statistically significant

Hormone
A substance produced by one part of the body that travels to another part of the body and causes a **physiological** effect

Hot flushes
Feeling of intense heat with sweating and rapid heartbeat that can occur as a symptom of the menopause, or as an adverse reaction to some medicines such as **tamoxifen**

Letrozole
An **aromatase inhibitor** given to treat breast cancer

Metabolised
The act of the body breaking down substances

Metabolism
The chemical processes or changes that occur in the body in order to maintain life. This involves either breaking down substances or making new ones

Metabolites
The products of **metabolism**

Oestrogen
A **hormone** that controls female sexual development. Some cancers such as breast cancer also depend on oestrogen to develop; therefore some treatments for these cancers involve drugs which decrease the amount of oestrogen in the body

Paroxetine
An antidepressant medicine belonging to the **SSRI** drug class

Placebo
Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

Progesterone
A **hormone** that prepares the body for pregnancy

P-value
A measure of the statistical probability of an event occurring by chance. Usually, a p-value of less than 0·05 suggests the event is statistically significant and did not occur by chance; a p-value of 0·05 or greater suggests the event is not statistically significant and occurred by random chance

Quinidine
A treatment for arrhythmia (an abnormal or irregular heartbeat)

Randomised, placebo-controlled clinical trial
A clinical trial in which the study participants are randomly assigned to receive a test medicine, or a **placebo** or comparator medicine

SSRI (Selective serotonin reuptake inhibitors)
A class of antidepressant drugs that work by altering the levels of certain neurotransmitters (brain chemicals), particularly serotonin

Sertraline
An antidepressant medicine belonging to the **SSRI** drug class

SNRI (Selective serotonin and noradrenaline reuptake inhibitor):
A class of antidepressant drugs that work by altering the levels of certain neurotransmitters (brain chemicals), particularly serotonin and noradrenaline

Tamoxifen
A selective oestrogen receptor modulator drug used to treat breast **cancer**

Venlafaxine
A class of antidepressant belonging to the **SNRI** drug class