Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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Recent data have further defined the established risk of QT interval prolongation with citalopram and escitalopram. This effect is now known to be dose-dependent. There are new restrictions on the maximum daily doses, including in elderly patients. Furthermore, citalopram and escitalopram should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval – see article A1 for full advice.

A number of cases of serious and fatal haemorrhage from Japan have been reported in elderly patients with renal impairment who were receiving the anticoagulant dabigatran. Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). See article A2 for further advice.

A substantial body of data from meta-analyses looking at a possible association between use of angiotensin II receptor antagonists (ARBs) and cancer has now accrued. Rather than supporting the original concerns raised for ARBs, the totality of the available evidence from well conducted analyses is reassuring and does not support any increased risk of cancer in patients using these medicines. Read more in our Hot topic.

Finally, try our end-of-year quiz to remind yourself of some of the key safety advice provided in 2011!

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Drug safety advice

A1 Citalopram and escitalopram: QT interval prolongation—new maximum daily dose restrictions (including in elderly patients), contraindications, and warnings

Citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval. ECG measurements should be considered for patients with cardiac disease, and electrolyte disturbances should be corrected before starting treatment. For citalopram, new restrictions on the maximum daily doses now apply: 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment.

For escitalopram, the maximum daily dose for patients older than 65 years is now reduced to 10 mg/day; other doses remain unchanged

Citalopram, a racemic mixture of R and S citalopram, is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depressive disorder, panic disorder, and obsessive compulsive disorder. Escitalopram is the S enantiomer of citalopram indicated for major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder, and obsessive compulsive disorder.

New data for QT prolongation with citalopram and escitalopram

The potential for citalopram and escitalopram to cause QT interval prolongation has been known for some time and is reflected in the product information. However, recent data have further defined this risk and have clarified that their effects on the QT interval are dose dependent. All available data have been subject to a Europe-wide review.

For both citalopram and escitalopram, elderly patients have a higher exposure due to age-related decline in metabolism and elimination. The maximum dose of both medicines has therefore been restricted in patients older than 65 years.

Citalopram

The data for citalopram include double-blind placebo-controlled electrocardiogram (ECG) studies. A study showed a clear dose-dependent response: the change from baseline in QTc (Fridericia-correction) was 7.5 milliseconds (90% CI 5.9–9.1) at 20 mg/day, and 16.7 milliseconds (15.0–18.4) at 60 mg day.

Escitalopram

For escitalopram a dose-dependent increase in QT interval was also shown: the change from baseline in QTc (Fridericia correction) was 4.3 (90% CI: 2.2–6.4) milliseconds with 10 mg/day and 10.7 milliseconds (90% CI: 8.6–12.8) with 30 mg/day.

Cases of QT prolongation and ventricular arrhythmia
Cases of QT prolongation and ventricular arrhythmia, including Torsade de Pointes (TdP), have been reported via the Yellow Card Scheme with citalopram and escitalopram, mainly in women, those with hypokalaemia, or in those with pre-existing QT prolongation or other cardiac diseases.

Article continues…

Drug interactions

Use with drugs known to prolong QT Interval
Citalopram and escitalopram may have an additive effect to other drugs that prolong the QT interval. Coadministration of citalopram and escitalopram with medicines that prolong the QT interval is therefore contraindicated. These include:

- class IA and III antiarrhythmics (eg, amiodarone, dronedarone, quinidine)
- antipsychotics (eg, fentiazine derviatives, pimozide, haloperidol)
- tricyclic antidepressants
- some antimicrobial agents (eg, sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalaria treatment—particularly halofantrine)
- some antihistamines (astemizole, mizolastine)
- some antiretrovirals (eg, ritonavir, saquinavir, lopinavir)

Use with drugs that increase escitalopram and citalopram levels

Patients taking concomitant medications known to increase plasma levels of escitalopram and citalopram may require a dose reduction in light of these most recent QT data. Drugs known to increase plasma concentrations of escitalopram and citalopram include some antiretroviral medications, and omeprazole and cimetidine. Details of specific interactions can be found in individual Summaries of Product Characteristics.

See http://www.medicines.org.uk/emc/ for Summaries of Product Characteristics

Advice for healthcare professionals:

Maximum daily dose schedule is as follows:

	Adults	Adults >65 years	Adults with hepatic impairment
Citalopram	40 mg*	20 mg*	20 mg*
Escitalopram	20 mg	10 mg*	10 mg

*New (restricted) maximum daily dose.

- Patients who currently take doses higher than the new recommended daily maximum should have their treatment reviewed

Contraindications in patients at greatest risk of QT interval prolongation:

- Citalopram and escitalopram should not be used:
  - in patients with congenital long QT syndrome or known pre-existing QT interval prolongation
  - in combination with other medicines known to prolong the QT interval (see above)

Cautions for use:

- The balance of benefits and risks of citalopram and escitalopram should be considered carefully, particularly at higher doses, in patients with pre-existing risk factors for QT interval prolongation—including patients with significant bradycardia; recent acute myocardial infarction; or decompensated heart failure

Monitoring recommendations:

- In patients with cardiac disease, an ECG review should be considered before treatment with citalopram and escitalopram
- Electrolyte disturbances (eg, hypokalaemia and hypomagnesaemia) should be corrected before treatment with citalopram and escitalopram. Monitoring of serum magnesium is advised, particularly in elderly patients, who may be taking diuretics or proton pump inhibitors
- If cardiovascular symptoms, such as palpitations, vertigo, syncope, or seizures develop during treatment, cardiac evaluation including an ECG should be undertaken to exclude a possible malignant cardiac arrhythmia

Further information:

BNF section 4.3.3 Selective serotonin re-uptake inhibitors: http://bnf.org/bnf/bnf/62/3351.htm?q=SSRI&t=search&ss=text&p=1

October and November reports of the European Pharmacovigilance Working Party: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/10/WC500117061.pdf and http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/11/WC500117988.pdf

See letter sent to healthcare professionals, Oct 2011 for citalopram): http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON134744]

Article continues….

- If QTc interval is >500 milliseconds, treatment should be withdrawn gradually
- If QTc interval duration is between 480 milliseconds and 500 milliseconds, the balance of benefits and risks of continued treatment should be carefully considered, alongside options for dose reduction or gradual withdrawal

Article citation: Drug Safety Update Dec 2001 vol 5, issue 5: A1.

A1 **Dabigatran (Pradaxa▼): risk of serious haemorrhage—need for renal function testing**

A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving dabigatran. Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min)

Dabigatran (Pradaxa▼) is a reversible inhibitor of free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. It is licensed for primary prevention of venous thromboembolic (VTE) events in adults who have had elective total hip replacement surgery or total knee replacement surgery (dose 220 mg/day), and for prevention of stroke and systemic embolism (SSE) in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors (dose 300 mg/day). Dabigatran has a rapid onset of action and does not require therapeutic monitoring. It is eliminated unchanged in urine. Exposure to dabigatran is substantially increased in patients with renal insufficiency.

Haemorrhage is a well recognised and common adverse reaction with dabigatran

To minimise the risk of bleeding, dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance, <30 mL/min). A dose reduction and close clinical surveillance should be considered in patients with moderate renal impairment (creatinine clearance 30–50 mL/min), particularly in those at increased risk of bleeding. Similar precautions are recommended for patients older than 75 years (for more specific details see Summary of Product Characteristics).

See http://www.medicines.org.uk/emc/ for Summaries of Product Characteristics

There is no specific antidote to dabigatran, and excessive anticoagulation may require interruption of treatment. In the event of haemorrhagic complications, treatment must be discontinued and the source of the bleeding investigated; adequate diuresis must be maintained.

Case reports of fatal haemorrhage in Japan

The receipt of a number of case reports of fatal haemorrhage in patients who received dabigatran for SSE in Japan has resulted in a strengthening of the advice for prescribers. All patients were reported to be older than 75 years, with renal impairment and additional risk factors for bleeding, including concomitant medication. All cases reportedly received the lower recommended dose of dabigatran (ie, 220 mg/day). Half the patients were also reported to have severe renal impairment, which is a contraindication for dabigatran therapy.

In addition to the measures already advised to reduce the risk of bleeding, renal function should also be assessed in all patients before starting dabigatran, and at least once a year thereafter in patients older than 75 years or in any patient with a suspected decline in renal function.

Article continues…

Further information:

See letter for healthcare professionals sent Oct 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON134744

BNF section 2.8.2 Oral anticoagulants: http://bnf.org/bnf/bnf/current/2791.htm

Advice for healthcare professionals:

- Do not start dabigatran in any patient with severe renal impairment (creatinine clearance <30 mL/min)
- Assess renal function:
  - in all patients before starting dabigatran
  - when a decline in renal function is suspected during treatment (eg, hypovolaemia, dehydration, or with some comedications)
  - at least annually in patients older than 75 years
  - at least annually in patients with renal impairment
- Check for signs of bleeding or anaemia and stop treatment if severe bleeding occurs

Anticoagulants and haemorrhage risk

It is important to remember that haemorrhage is a well recognised adverse outcome of any anticoagulant, and all patients at increased risk of bleeding require close clinical monitoring.

Warfarin

For warfarin, a dose reduction in elderly people should be considered, and increased frequency of INR monitoring in patients at high risk of bleeding—including those with renal insufficiency—is advised. Many foods and some drugs interact with warfarin, affecting prothrombin time, and therefore patients with changes to their medication may also require extra INR monitoring. Those at high risk of bleeding may benefit from dose adjustment and shorter duration of therapy.

Rivaroxaban

For rivaroxaban (Xarelto▼), caution is required in patients with severe renal impairment (creatinine clearance <30 mL/min) or moderate hepatic impairment. It is not recommended in patients with a creatinine clearance of less than 15 mL/min. Rivaroxaban is also contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, and is not recommended in those also taking strong inhibitors of cytochrome P 3A4 enzyme or P-glycoprotein, such as the azole-antimycotics (eg, ketoconazole) or HIV protease inhibitors (eg, ritonavir).

Article citation: Drug Safety Update Dec 2011 vol 5, issue 5: A2.

Hot topic

H1 **Angiotensin II receptor antagonists: evidence does not suggest any link with cancer**

A substantial body of data looking at a possible association between use of **angiotensin II receptor antagonists** and cancer has now accrued. The totality of

Angiotensin II receptor antagonists (ARBs) are an important option in the treatment of hypertension.

In 2010, a meta-analysis of randomised controlled trials by Sipahi and colleagues[1] reported a small but significant association between use of ARBs and new cancer occurrence, particularly lung cancer. This study had several methodological limitations

the available evidence from well conducted analyses is reassuring and does not support any increased risk of cancer in patients who use these medicines

and it sparked further investigation of the issue by several other independent investigators.

Since then, the results of three further meta-analyses have become available.[2–4] These analyses include most of the available data from randomised controlled trials and, although they were conducted differently, all have very similar findings. Importantly, none suggest an association with cancer.

The findings from the meta-analyses of randomised controlled trials are largely supported by the findings of two large observational studies.[5,6] Although some subgroup analyses and individual trials showed a modest increase or decrease in risk, these findings were inconsistent across trials or analyses.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed a possible link between the use of ARBs and the occurrence of new cancers and concluded that the evidence does not support any increased risk of cancer in patients who use these medicines. Rather than supporting the original concerns raised for ARBs, the totality of the available evidence from well conducted analyses is reassuring and does not support any increased risk of cancer.

References:
1 Sipahi et al. Lancet Oncol 2010; 11: 627–36.
2 Bangalore et al. Lancet Oncol 2011; 12: 65–82.
3 ARB Trialists Collaboration. J Hypertens 2011; 29: 623–35.
4 US Food and Drug Administration. Statistical review - meta-analysis, clinical studies. 2011. Ref ID: 2940354.
5 Pasternak et al. Circulation 2011; 123: 1729–36.
6 Chang et al. J Clin Oncol 2011; 29: 3001–07.

Further information:
European Medicines Agency press release:
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/10/WC500116865.pdf

BNF section 2.5.5 Drugs affecting the renin-angiotensin system:
http://bnf.org/bnf/bnf/current/27510.htm?q=renin&t=search&ss=text&p=2#_hit

US Food and Drug Administration drug safety announcement:
http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm#data

Article citation: Drug Safety Update Dec 2011 vol 5, issue 5: H1.

Other information from the MHRA

O1 Learning about reducing medicines risk

See
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/SSRIlearningmodule/index.htm

We have recently launched a learning module on **SSRI antidepressants** for clinical practitioners.

This self-directed learning package outlines the key risks of this important class of medicines. For each adverse effect, the package outlines:

- The main features of the adverse effect
- Factors that increase the risk
- How the risk can be reduced
- Specific treatment for the adverse effect

A self-assessment exercise, together with full feedback, complements the learning material.

This learning package is suitable for doctors, pharmacists, and nurses involved in the care of patients with depression. Clinicians starting out in psychiatry will find it especially valuable.

Article continues….

See
http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/pharmacovigilancelearningmodule/index.htm

Pharmacovigilance

We are delighted that our learning package on pharmacovigilance, introduced in May 2011, has recently been accredited by the Faculty of Pharmaceutical Medicine for three Continuing Professional Development (CPD) credits. This award follows endorsement of the package by the Royal College of Nursing.

The module has attracted a very encouraging number of visitors; the possibility of gaining CPD credits makes it even more attractive.

Article citation: Drug Safety Update Dec 2011 vol 5, issue 5: O1.

End-of-year quiz

Do you read Drug Safety Update every month? Then test your knowledge of drug safety in our annual quiz.

If you participate in Continuing Professional Development/Continuing Medical Education, you may be able to use the completed quiz as evidence of learning through reading of Drug Safety Update. To claim personal CPD points in this way, we suggest you keep a copy of the quiz, together with your answers and the bulletin articles.

The answers are given overleaf.

An answer can be regarded as correct if one part of the whole question is answered correctly. Some articles in Drug Safety Update are more relevant for some healthcare professionals than for others, so feel free to attempt only the questions related to your specialty!

Please do not send your answers to us, this quiz is just for fun!

Questions

1 Treatment with **bevacizumab** or **sunitinib** may increase the risk of development of osteonecrosis of the jaw, particularly in patients who previously received or are treated concurrently with bisphosphonates. What course of action should be taken before treatment?

2 The immunomodulatory agents **lenalidomide** and **thalidomide** for treatment of myeloma are associated with an increased risk of arterial and venous thromboembolism. What action should be taken to minimise this risk?

3 Modafinil is indicated for treatment of excessive sleepiness in adults with narcolepsy. Which adverse events should lead to permanent treatment discontinuation?

4 People with schizophrenia are three times more likely to die prematurely from natural causes (mainly cardiovascular) compared with people without mental health disorders. What support should be given to patients during treatment with **atypical antipsychotics** to minimise their risks?

Quiz continues….

5 Atypical femoral fractures have been reported rarely with **bisphosphonate** therapy, mainly in patients receiving long-term treatment for osteoporosis. What are the warning symptoms for such fractures, and what course of action should be taken in patients with a suspected atypical femur fracture?

6 Use of **pioglitazone** is associated with a small increased risk of which cancer type? For which subgroup of patients is pioglitazone now contraindicated because of this risk?

7 What is the serious and potentially fatal risk associated with concomitant use of **systemic fusidic acid and a statin**?

8 What is the new and restricted indication for **dronedarone** (Multaq)?

9 What are the new maximum daily dose recommendations for elderly patients (ie, >65 years) for (a) **citalopram** and (b) **escitalopram**?

10 Where can you report a suspected adverse drug reaction?

Answers are given overleaf!

Quiz answers

1 Dental examination and appropriate preventative dentistry should be considered before start of treatment. Invasive dental procedures should be avoided if possible in patients being treated with bevacizumab who have previously received, or who are receiving, bisphosphonates.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON105745

2 Minimise all modifiable risk factors for thromboembolic events (ie, smoking, hypertension, hyperlipidaemia). Consider antithrombotic prophylaxis as recommended.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON108684 and http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON123111

3 Serious skin or hypersensitivity reactions; and psychiatric disorders such as suicidal ideation.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON111502

4

- Early identification of modifiable risk factors (eg, smoking and diet)
- Monitoring for development of metabolic adverse effects (eg, weight gain, dyslipidaemia, and hyperglycaemia) and appropriate management of these.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON111764

5 *Warning symptoms:* These fractures can occur after minimal or no trauma. Some patients have thigh or groin pain, often associated with features of stress fractures on radiograph, weeks to months before presenting with completed femoral fracture. Poor healing of these fractures also reported.
Course of action: Bisphosphonate treatment should be stopped while the suspected fracture is evaluated, and should be based on an assessment of the benefits and risks of treatment for the individual. The contralateral femur should be examined because these fractures are commonly bilateral.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON120213

6 Bladder cancer: patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON125962

7 Risk of rhabdomyolysis: systemic fusidic acid should not be given with statins. In patients for whom systemic fusidic acid is essential, statin treatment should be temporarily discontinued throughout the duration of fusidic acid treatment.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON128951

Answers continue overleaf….

8 Maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON131928

9 (a) 20 mg/day for citalopram
(b) 10 mg/day for escitalopram.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137769

10 Report suspected adverse drug reactions via the Yellow Card Scheme—the simplest way to report is via www.mhra.gov.uk/yellowcard

Article citation: Drug Safety Update Dec 2011 vol 5, issue 5: O2.