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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Safety reviews of some important medicines have recently been completed, and this month's Drug Safety Update summarises what they mean for your practice. A review of methylphenidate has confirmed the benefits of this medicine when used within its licensed indication to treat ADHD in children age 6 years or older and adolescents. However, prescribing information is being updated with further guidance, particularly on cardiac monitoring, to support safer use—see p 2 for more information. Page 4 also updates you on a recent assessment of another drug for ADHD, atomoxetine, with information about the potential for nervous-system or psychiatric side-effects.

Antipsychotic medicines (both typical conventional and atypical) in elderly people with dementia are associated with a clear increased risk of stroke and a small increased risk of death. Read our latest advice for these medicines on p 5.

We also have important information about a risk of atypical stress fracture with alendronic acid (p 8), and on the risk of severe pancreatitis with the diabetes treatment exenatide (p 6).

Also this month, the Yellow Card Scheme update reviews suspected adverse reaction data we have received on the reaction progressive multifocal leukoencephalopathy (p 9, see also p 13 for news on this risk with efalizumab, leading to a recommendation to suspend its marketing authorisation). And our Hot topic (p 11) shows some revealing statistics about the public's views on herbal medicines.

Claire Tilstone, Editor

drugsafetyupdate@mhra.gsi.gov.uk

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.

Drug safety advice

Methylphenidate: updated guidance on safe and effective use in ADHD

Keywords: methylphenidate, attention deficit/hyperactivity disorder, ADHD, cardiovascular, cerebrovascular, psychiatric

The benefits of methylphenidate continue to outweigh the risks when used to treat ADHD in children aged 6 years or older and adolescents. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Patients should be monitored during treatment, which should be interrupted at least once a year to determine whether continuation is needed

For further information, see the EMEA's website for: press release at http://www.emea.europa.eu/pdfs/human/referral/methylphenidate/2231509en.pdf; question-and-answer document at http://www.emea.europa.eu/pdfs/human/referral/methylphenidate/MethylphenidateQ&A_65828508en.pdf; and Summary of Product Characteristics at http://www.emea.europa.eu/pdfs/human/referral/methylphenidate/4461609en.pdf

Further information on brands of methylphenidate available in the UK, see BNF, p 216 (edn 56; www.bnf.org).

Information on DSM-IV criteria is at http://www.psychiatryonline.com/; information on ICD-10 is at http://www.cdc.gov/nchs/about/otheract/icd9/abticd10.htm

The European Medicines Agency (EMEA) has completed a review of the benefits and risks of methylphenidate after recent concerns about its cardiovascular, cerebrovascular, and psychiatric safety and its long-term effects.

The EMEA's Committee for Medicinal Products for Human Use concluded that on the basis of currently available data, the benefits of methylphenidate continue to outweigh the risks when used in its licensed indication. Methylphenidate is indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years or older and adolescents, who are diagnosed according to DSM-IV criteria or guidelines in ICD-10 and when remedial measures alone are insufficient.

Key safety information and advice for healthcare professionals:

Contraindications—methylphenidate should not be used in patients with:

For further information on contraindications, see http://www.emea.europa.eu/pdfs/human/referral/methylphenidate/4461609en.pdf

- Diagnosis or history of severe depression, anorexia nervosa or anorexic disorders, suicidal tendencies, psychotic symptoms, mania, schizophrenia, severe mood disorders, or psychopathic or borderline personality disorder
- Diagnosis or history of severe and episodic (type I) bipolar (affective) disorder that is not well-controlled
- Pre-existing cerebrovascular disorders—eg, cerebral aneurysm and vascular abnormalities, including vasculitis or stroke
- Unless specialist cardiac advice has been obtained: in pre-existing cardiovascular disorders, including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias, and dysfunction of cardiac ion channels

Pretreatment screening

- Before prescribing, the patient's baseline cardiovascular status, including blood pressure and heart rate, should be assessed

- A complete history should be taken, documenting: concomitant medicines; past and present medical and psychiatric disorders or symptoms; family history of sudden cardiac death, unexplained death, or malignant arrhythmia; and accurate pretreatment height and weight on a growth chart. Patients who are being considered for treatment with methylphenidate should also have physical examination for the presence of heart disease
- Patients should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Caution should be used when treating patients whose underlying medical conditions might be compromised by increased blood pressure or heart rate

Ongoing monitoring

- Blood pressure and pulse should be recorded on a centile chart at every dose adjustment and then at least every 6 months
- Height, weight, and appetite should be recorded at least every 6 months on a growth chart
- Methylphenidate could cause or worsen some psychiatric disorders such as depression, suicidal thoughts, hostility, anxiety, agitation, psychosis, and mania. Development of new, or worsening of pre-existing, psychiatric symptoms should be monitored at every dose adjustment and then at least every 6 months, and at every visit
- Prescribers should look out for signs of diversion (transfer of the medicine from the individual for whom it was prescribed to one for whom it is not prescribed), misuse, and abuse of methylphenidate
- Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea, or other symptoms suggestive of heart disease during methylphenidate treatment should undergo prompt specialist cardiac evaluation

There is a lack of data on the long-term effects of methylphenidate. For patients who take methylphenidate for extended periods (ie, >1 year), physicians should periodically interrupt treatment at least once a year to determine whether continuation is necessary. The longer-term safety of methylphenidate remains under close review, and the results of ongoing studies to better characterise the known or potential risks of ADHD medicines will be evaluated when available.

NICE guidance

See http://www.nice.org.uk/guidance/index.jsp?action=byId&o=12061 for NICE guidance.

NICE recommends that in school-age children and young people, drug treatment should be offered as first-line treatment in severe ADHD and severe impairment.

Atomoxetine: risk of psychotic or manic symptoms

Keywords: atomoxetine, Strattera, attention deficit/hyperactivity disorder, ADHD, psychiatric disorders, psychotic reactions, hallucination, mania, agitation, delusion

Atomoxetine is associated with treatment-emergent psychotic or manic symptoms in children and adolescents without a history of such disorders. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine and discontinuation of treatment

Atomoxetine (Strattera) is a selective noradrenaline reuptake inhibitor, authorised since 2004 for use in the treatment of attention-deficit/hyperactivity disorder (ADHD) as part of a comprehensive treatment regimen.

Continued case reports of possible nervous-system and psychiatric adverse effects prompted a review of data from all sources, resulting in updated information on the risk of new-onset or worsening of serious psychiatric disorders, including psychotic reactions, hallucinations, mania, and agitation. Product information for prescribers has been updated to reflect more fully the emerging safety information.

Access the Summary of Product Characteristics at http://emc.medicines.org.uk/

Advice for healthcare professionals:

- At normal doses, atomoxetine can be associated with treatment-emergent psychotic or manic symptoms (eg, hallucinations, delusional thinking, mania, or agitation) in children and adolescents without a history of psychotic illness or mania
- If such symptoms occur, consideration should be given to a possible causal role of atomoxetine and discontinuation of treatment
- It remains possible that atomoxetine might exacerbate pre-existing psychotic or manic symptoms

Antipsychotics: use in elderly people with dementia

Keywords: antipsychotics, atypical, conventional (typical), risperidone ▼, dementia, Alzheimer's, aggression, elderly, mortality, stroke, cerebrovascular

There is a clear increased risk of stroke and a small increased risk of death when antipsychotics (typical or atypical) are used in elderly people with dementia

Use of antipsychotics in dementia

Only one antipsychotic, risperidone (Risperdal ▼), is licensed for treatment of dementia-related behavioural disturbances: and then only specifically for short-term (up to 6 weeks') treatment of persistent aggression in Alzheimer's dementia unresponsive to non-pharmacological approaches and where there is a risk of harm to the patient or others. Elderly people with dementia are at risk from specific serious and life-threatening side-effects when treated with antipsychotics.

Risk of stroke

In 2004 the Committee on Safety of Medicines (the predecessor to the Commission on Human Medicines) advised of a clear increase in the risk of stroke with the use of the atypical antipsychotics risperidone ▼ or olanzapine in elderly people with dementia (approximately three-times increased risk compared with placebo), and that the magnitude of risk outweighed any likely benefit of treating dementia-related behavioural problems with these drugs. A year later a Europe-wide review concluded that this risk could not be excluded for other antipsychotics (atypical or typical), and the product information for all antipsychotics was updated to include a class warning.

Increased mortality

In 2005 an analysis of 17 placebo-controlled trials found that atypical antipsychotics are associated with increased mortality when used in elderly people with dementia (about 1–2% increased risk compared with no treatment).[1] For risperidone, there is an additional increase in the risk when coprescribed with furosemide.

Subsequently in November 2008, a European assessment of published observational data concluded that a similar increased risk of death could not be excluded for the typical (conventional) antipsychotics.[2,3]

About risperidone ▼

In the case of persistent aggression in moderate to severe Alzheimer's disease, where the patient puts themselves or others at risk of harm, short-term treatment with risperidone ▼ may be indicated if the behaviour has not responded to non-pharmacological means. A new analysis of three randomised control trials[4–6] conducted in behavioural problems in the elderly showed a clear benefit for the short-term use of risperidone ▼ when aggression only was considered. The balance of risks and benefits for risperidone ▼ use to treat behavioural disturbances in dementia is only considered to be positive within its narrow licensed indication: ie, short-term use for persistent aggression in Alzheimer's-type dementia.

1 US FDA Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioural disturbances, April 11 2005. http://www.fda.gov/cder/drug/advisory/antipsychotics.htm (accessed Jan 29, 2009).

2 Schneeweiss S, et al. *CAMJ* 2007; **176:** 627–32.

3 Gill SS, et al. *Ann Intern Med* 2007; **146:** 775–86.

See also statement from the European Medicines Agency at http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_Antipsychotics_Article5.3-CHMP_Opinion.pdf and accompanying report and question-and-answer document at http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_%20Antipsychotics_Article5.3-Appendix1-CHMPAR.pdf and http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_antipsychotics_Article_5.3-Q&A.pdf

4 Katz IR, et al. *J Clin Psychiatry* 1999; **60:** 107–15.

5 De Deyn PP, et al. *Neurology* 1999; **53:** 946–55.

6 Brodaty H, et al. *J Clin Psychiatry* 2003; **64:** 134–43.

See also http://www.emea.europa.eu/pdfs/human/referral/Risperdal/risperdal_bi_en.pdf and http://www.emea.europa.eu/pdfs/human/referral/Risperdal/risperdal_annexI_IV_en.pdf, p 48.

Further information

National Dementia Strategy, published Feb 3, 2009: http://www.dh.gov.uk/en/socialcare/deliveringadultsocialcare/olderpeople/nationaldementiastrategy/index.htm

For further information on non-pharmacological interventions, see **NICE guidance** http://www.nice.org.uk/Guidance/CG42

The **dementia antipsychotic withdrawal trial** (DART-AD): long-term follow-up of a randomised controlled trial. Ballard C, et al. *Lancet Neurol* 2009; **8:** 151–57.

Exposure to **antipsychotics and risk of stroke**: self controlled case series study. Douglas IJ and Smeeth L. *BMJ* 2008; **337:** a1227.

MHRA information on antipsychotics: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Productspecificinformationandadvice/Antipsychoticdrugs/index.htm

Royal College of Psychiatrists: http://www.rcpsych.ac.uk/

Alzheimer's Society: http://alzheimers.org.uk/site/index.php

Alzheimer's Research Trust: http://www.alzheimers-research.org.uk/

Risperdal Summary of Product Characteristics: http://emc.medicines.org.uk/

Complete a Yellow Card online at www.yellowcard.gov.uk

For more information on the Black Triangle Scheme see http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Medicines/Reportingsuspectedadversedrugreactions/Healthcareprofessionalreporting/BlackTriangleScheme/index.htm

Advice for healthcare professionals:

- There is a clear increased risk of stroke and a small increased risk of death when antipsychotics (typical or atypical) are used in elderly people with dementia
- The balance of risks and benefits associated with risperidone ▼ treatment should be carefully assessed for every patient, taking into consideration the known increased mortality rate associated with antipsychotic treatment in the elderly. Prescribers should carefully consider the risk of cerebrovascular events before treating with risperidone ▼ any patient who has a previous history of stroke or transient ischaemic attack. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, smoking, and atrial fibrillation

Risperidone: new Black Triangle (▼) status

The Black Triangle Scheme identifies medicines whose safety profiles are monitored intensively by MHRA and CHM. Risperidone ▼ has been added to the list of black triangle medicines after the granting of the new narrow indication in Alzheimer's dementia as outlined above. Healthcare professionals are asked to please report via the Yellow Card Scheme all suspected side-effects to risperidone ▼ that occur when it is used to treat elderly people with dementia. You do not have to be certain of causality—if in doubt, please report.

Exenatide (Byetta ▼): risk of severe pancreatitis and renal failure

Keywords: exenatide, Byetta ▼, incretin mimetic, type 2 diabetes, pancreatitis, renal impairment

Suspected adverse reaction reports of necrotising and haemorrhagic pancreatitis have been received in association with exenatide. Some of these reports had a fatal outcome. If pancreatitis is diagnosed, exenatide should be permanently discontinued. Reports of renal impairment, including acute renal failure and worsened chronic renal failure have also been received. Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment

Exenatide (Byetta ▼), the first-in-class incretin mimetic, is a glucagon-like-peptide-1 analogue that stimulates insulin release from pancreatic β cells in a glucose-dependent manner.

Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with metformin, with or without sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. Exenatide should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. It should not be used in patients with type 2 diabetes who require insulin therapy due to β-cell failure.

Treatment with exenatide should be initiated at 5 µg twice daily for at least 1 month to improve tolerability. The dose can then be increased to 10 µg twice daily to further improve glycaemic control. Doses higher than 10 µg twice daily are not recommended.

Pancreatitis

See Drug Safety Update May 2008, p 5; www.mhra.gov.uk/mhra/drugsafetyupdate

Exenatide was first marketed in the EU in November 2006 and since then the MHRA in conjunction with the European Medicines Agency (EMEA) has monitored its safety. Acute pancreatitis is a known adverse effect of exenatide, but continued reporting of serious and fatal cases has led to re-evaluation of this issue.

*Data derived from IMS Disease Analyzer 10/07–09/08 by the MHRA.

An estimated 8000 patients in the UK were prescribed exenatide in the 12-month period up to September 2008 and usage is increasing rapidly (source: IMS Disease Analyzer*). Up to February 2009, we have received six case reports of pancreatitis and a further three cases of acute pancreatitis in the UK. There have been approximately 800 000 patient-years of exposure worldwide since licensing. 396 case reports of pancreatitis have been received worldwide in association with exenatide up to September 2008 (mostly from the USA). 80% of these reports were considered to be possibly related to exenatide, and in several cases there was evidence of positive rechallenge. Nine reports of necrotising or haemorrhagic pancreatitis have been received worldwide, two of which had a fatal outcome. After a Europe-wide review, product information for exenatide is being updated to contain further information about this risk.

Renal impairment

Case reports of renal impairment, including several UK reports of renal failure, have been received in association with exenatide. Up to Jan 30, 2009 we have received seven case reports of acute renal failure in the UK. This medicine is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Clinical experience in patients with moderate renal impairment is very limited.

Advice for healthcare professionals:

- There have been reports of necrotising and haemorrhagic pancreatitis with exenatide, some of which were fatal
- If pancreatitis is suspected, treatment with exenatide should be suspended immediately; if pancreatitis is diagnosed, exenatide should be permanently discontinued
- Diagnosed pancreatitis with an unexpectedly prolonged course, haemodynamic instability, fever, failure of medical therapy, or presence of fluid collections on CT suggest possible necrosis
- Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min)

Further reading

Diagnosis and management of acute pancreatitis: Munoz A, Katerndahl DA. *Am Fam Physician* 2000; **62:** 164–74.

Pancreatic necrosis and pancreatic abscess: Thomson ABR, Frizzell ER. 2008, http://emedicine.medscape.com/article/181264-overview (accessed Jan 22, 2009).

Reporting of suspected adverse reactions to exenatide ▼

As with all medicines, the safety of exenatide remains under close review. Please continue to report to the MHRA and the Commission on Human medicines all suspected adverse reactions to exenatide via the Yellow Card Scheme at www.yellowcard.gov.uk

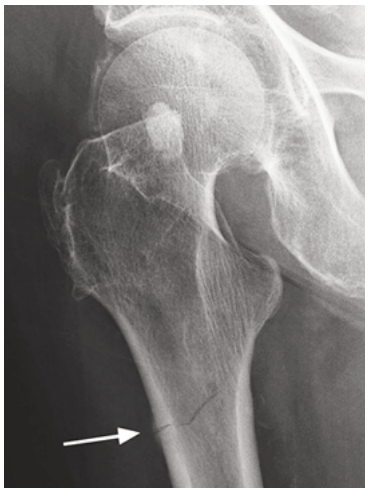
Bisphosphonates: atypical stress fractures

Keywords: bisphosphonates, alendronic acid, osteoporosis, Paget's disease, atypical stress fracture

Atypical stress fractures of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid. Patients who develop stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits for the individual clearly outweigh the risk of harm. An increased risk of atypical stress fractures with other bisphosphonates cannot be excluded

Individual bisphosphonates have different indications, and are used for: prophylaxis and treatment of osteoporosis; treatment of Paget's disease; and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma. Recent evidence from published literature suggests that long-term use of alendronic acid may be associated with an increased risk of atypical stress fractures.[1–3] A Europe-wide review of bisphosphonates and atypical stress fractures has analysed preclinical data, clinical-trial data, postmarketing spontaneous reports of adverse drug reactions, published literature, and information from other drug regulatory authorities. The conclusions of the review are given below.

1 Kwek EB, et al. *Injury* 2008; **39:** 224–31.
2 Lenart BA, et al. *N Engl J Med* 2008; **358:** 12.
3 Neviaser AS, et al. *J Orthop Trauma* 2008; **22:** 346–50.



Radiograph of subtrochanteric stress fracture (see Kwek EBK, et al. *N Engl J Med* 2008; **359:** 316–18).

Information and advice for healthcare professionals:

Alendronic acid

- Atypical stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (in most cases, time to onset ranged from 18 months to 10 years)
- Fractures occurred after minimal or no trauma, and some patients experienced thigh pain weeks to months before presenting with a completed femoral fracture. Fractures were frequently bilateral; therefore the contralateral femur should be examined in patients treated with alendronic acid who have a femoral shaft fracture. Poor healing of these fractures was also reported
- Patients who develop atypical stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits of continued treatment are thought to clearly outweigh the risks to the individual
- Product information for alendronic acid will be updated to include a warning about atypical stress fractures

All other bisphosphonates

- Limited data are available for the other bisphosphonates in support of a causal association with atypical stress fractures. This might reflect their lower usage and the limited long-term data that exist for other bisphosphonates
- The possibility that other bisphosphonates may be associated with an increased risk of atypical stress fractures cannot be excluded
- The risk of atypical stress fractures with all bisphosphonates will be kept under close review, including consideration of further epidemiological research and further information will be issued for healthcare professionals when available

Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions in the UK. See www.yellowcard.gov.uk

Adverse drug reactions in focus: progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare and usually fatal re-infection of the CNS, characterised by progressive damage and inflammation of the white matter in the brain, in multiple locations.

PML is caused by a type of human polyoma virus known as the JC, or John Cunningham virus. The JC virus is widespread, with about 70–90% of adults presenting antibodies.

The virus usually remains latent in healthy individuals, only causing disease when the immune system is severely compromised. PML has been studied in patients with HIV infection, where incidence is approximately 5% of the disease population. PML also occurs in patients with cancer and those who have received kidney or bone-marrow transplants.

In PML, gradual destruction of the myelin sheath covering nerve axons leads to impaired transmission of nerve impulses. PML causes rapidly progressive focal neurological deficits including: cognitive and behavioural changes; paraesthesia; visual problems; gait abnormalities and loss of limb coordination; and hemiparesis.

Drugs associated with PML

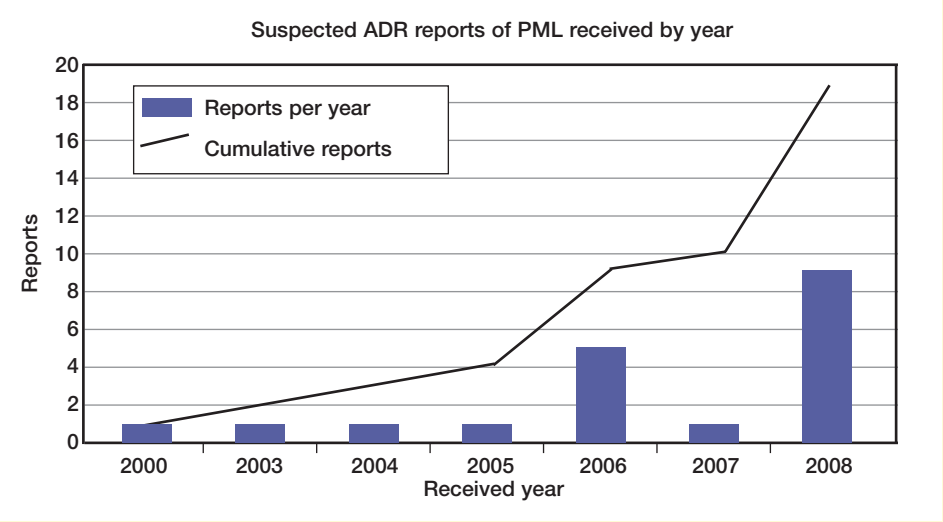
See Drug Safety Update September 2008, p 7 for information about natalizumab and December 2008, p 3 for information about rituximab; www.mhra.gov.uk/mhra/drugsafetyupdate

The MHRA has previously identified an association between PML and use of some monoclonal antibodies such as natalizumab (Tysabri ▼, used to treat multiple sclerosis) and rituximab (MabThera, indicated for non-Hodgkin's lymphoma and severe active rheumatoid arthritis). An association has also been identified between PML and efalizumab (Raptiva ▼, a treatment for moderate to severe plaque psoriasis). A European review has concluded that the benefits of this drug do not outweigh its risks, and the European Medicines Agency has recommended the suspension of the marketing authorisation for efalizumab.

See Stop press p 13.

Yellow Card reports for PML

Up to Jan 6 2009, the MHRA has received 19 suspected reports of PML, in three of which PML was listed as the fatal suspected reaction.



Yellow Card Scheme update *cont.*

The table lists the drugs most reported to the MHRA in association with suspected PML:

Suspected drug	Number of cases PML*
Cyclophosphamide (antineoplastic agent)	5
Rituximab (monoclonal antibody)	5
Epirubicin (antineoplastic agent)	3
Fludarabine (antineoplastic agent)	3

*Note that more than one drug may be implicated in a case of PML.

Warnings about PML are given in the product information for rituximab, alemtuzumab, natalizumab, fludarabine, nelarabine, and mycophenolate mofetil. There is currently insufficient evidence of a causal relation between cyclophosphamide or epirubicin and PML, and PML is not currently listed in the product safety information for these drugs. The risk of drug-induced PML continues to be monitored closely by the MHRA.

Please report suspected reactions of PML

Spontaneous reporting has provided important information in the identification of PML associated with some drugs. If you suspect the involvement of a drug in a case of PML, please let us know by filling in a Yellow Card. We are particularly interested in the time to onset of PML after starting treatment, indications for suspected drugs, and all other medicines the patient is receiving.

If in doubt, please report!

See www.yellowcard.gov.uk

Hot topic

Many healthcare professionals often encounter patients who are taking herbal medicines. In 2008 MHRA commissioned Ipsos MORI to research the public's perception of herbal medicines. The findings may help doctors and pharmacists when considering how to advise their patients

Public perception of herbal medicines

35% of adults say they have ever taken herbal medicines (26% have done so in the past 2 years). 29% of adults have used an over-the-counter herbal medicine; 5% have used traditional Chinese medicine (TCM) supplied by a TCM practitioner, clinic, or shop; and 8% a herbal medicine supplied by other herbal or traditional practitioner.

Perceptions on safety issues

When asked what advice on potential risks or possible problems should be given to a friend of family member considering using herbal medicines 36% of adults questioned said they are unaware of any possible problems or risks to look out for. The risk most commonly identified unprompted was that some herbal medicines have side effects (12%); the risk of interactions with conventional medication was identified by 6%; no other single risk was identified by more than 6%.

Information and trust

Qualitative findings suggest that the public generally are not very discerning about who they would approach for advice on herbal medicines—anyone with an interest in the subject, be they friends, family, or shop assistant was trusted to give good advice:

- 17% and 9% of adults questioned have ever used a doctor or pharmacist, respectively, as a source of information about herbal medicines
- 15% and 13% of adults have ever used family or friends/colleagues/workmates, respectively, as source of information
- When asked which one source of advice they would most trust about herbal medicines, 44% said a doctor and 14% a pharmacist; the next highest were herbal/traditional medicine practitioner (8%) and family (5%)
- 4% of adults have ever used product information included with the packaging as a source of information about herbal medicines (compared with 27% for all medicines in an Ipsos MORI survey for MHRA in 2006)

Regulation

29% of British adults believe herbal medicines are currently regulated in the UK, whereas 31% believe they are not, and 30% do not know. 10% believe that some herbal medicines are regulated, and some are not.

TCMs

Users of TCMs are more likely (76%) than any other group of users or non-users to believe that natural means safe. They are also more likely (44%) than other groups of users to believe that products were regulated. The qualitative research suggests that TCM practitioners may be heavily trusted by some users, with some participants suggesting that TCM is suitable for more serious medical conditions.

Technical information about the research

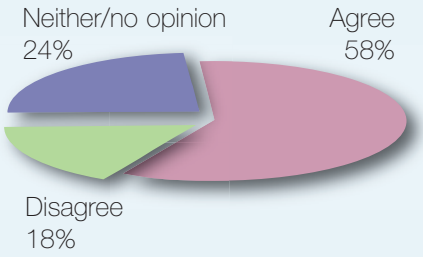
General public qualitative research: four discussion groups were conducted in July 2008 at two locations (Stockport and Croydon). Two groups were conducted in each location, one with users, and one with non-users of herbal medicines.

General public quantitative research: Questions were placed on the Ipsos MORI Omnibus. A nationally representative quota sample of 2305 adults (aged 15 years or older) was interviewed in 197 sampling points throughout Great Britain. Interviews were carried out face-to-face in respondents' homes. Fieldwork was conducted in September 2008. Data are weighted to match the profile of the Great Britain adult population.

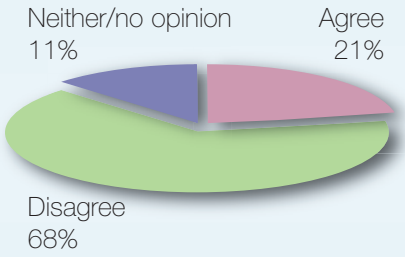
Key findings from adult herbal medicines users in past 2 years:

"To what extent do you agree/disagree with the statement that...

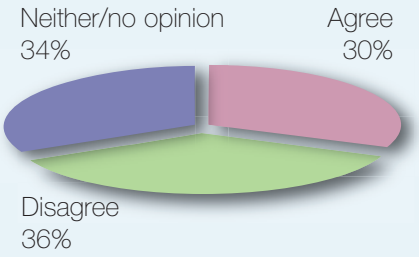
...herbal medicines are safe because they are natural?"



... when you visit your GP there is no need to tell them if you are taking a herbal medicine?"



... it's ok to use herbal medicines at the same time as conventional medicines?"



From MHRA homepage (www.mhra.gov.uk) use A-Z index to find information about Herbal Medicines Advisory Committee.

Reporting of adverse reactions

All medicines, including herbal remedies, have the potential to cause side effects. If a patient experiences an adverse reaction suspected to be associated with the use of a herbal medicine please submit a **Yellow Card:** www.yellowcard.gov.uk

See http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/HerbalSafetyNews/Currentsafetyissues/index.htm

See Drug Safety Update April 2008, p 7; www.mhra.gov.uk/mhra/drugsafetyupdate

From MHRA homepage (www.mhra.gov.uk) use A–Z index to find Public Assessment Reports for herbal medicines. These reports contain copies of the Summary of Product Characteristics and patient leaflet.

Advice for healthcare professionals from the Herbal Medicines Advisory Committee:

Patient vulnerability

- Be aware that:
  - Patients may be obtaining information from unreliable sources; they may be particularly vulnerable to some inexpert or unscrupulous operators in the unlicensed sector who may promote the belief that "natural" means "safe" to discourage scrutiny of the safety and quality of their products
  - Some herbal medicine users, of TCMs in particular, may be taking unlicensed herbal medicines for serious medical conditions. The MHRA continues to find evidence of TCMs and other unlicensed herbal products illegally containing potent and toxic undeclared ingredients

Informed choice of products made to assured standards

- For patients who wish to use herbal medicines there is now a growing range of regulated herbal medicines under the traditional herbal registration (THR) scheme that meet assured standards of safety, quality, and patient information. Agreed minor indications are permitted on the basis of traditional use. These products can be identified by the THR number on the packaging. Alongside these are herbal medicines with a product licence (PL) which also meet assured standards

Advice available

- For THRs a copy of the Summary of Patient Characteristics and patient leaflet is available on the MHRA website

Stop press

Efalizumab (Raptiva ▼): recommendation to suspend marketing authorisation

The European Medicines Agency has completed a review of **efalizumab (Raptiva ▼)** after concerns about its safety. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of efalizumab do not outweigh its risks, and that the marketing authorisation should be suspended across the EU.

Efalizumab is used to treat adults with moderate to severe chronic plaque psoriasis (a disease that causes red, scaly patches on the skin) who have not responded to, or who are unable to take, other treatments for psoriasis (including ciclosporin, methotrexate, and PUVA).

This medicine was reviewed after reports of serious side effects, including three confirmed cases of progressive multifocal leukoencephalopathy (PML) in patients who had received efalizumab for more than 3 years; two of these patients died.

Advice for healthcare professionals:

- Prescribers should not issue any prescriptions for efalizumab to patients who are not already taking it
- Prescribers should review the treatment of all patients who are currently taking efalizumab, with a view to stopping treatment
- Treatment with efalizumab should not stop abruptly (which could cause psoriasis to return or worsen). Prescribers should consider alternative treatments and continue to monitor the patient's psoriasis
- Efalizumab's effects on the immune system last for about 8–12 weeks. Healthcare professionals should closely monitor patients for infections and neurological symptoms after stopping treatment

Further information is available on the European Medicine Agency's website: see press release at http://www.emea.europa.eu/humandocs/PDFs/EPAR/raptiva/2085709en.pdf and question and answer document at http://www.emea.europa.eu/humandocs/PDFs/EPAR/raptiva/RaptivaQ&A_1552509en.pdf

Patient-controlled analgesia extension sets: risk of inadequate pain relief

We have issued a medical device alert to highlight the risk of inadequate pain relief with **Wescott Medical Sae-Flow patient-controlled analgesia extension sets**. An error during assembly caused leakages in some sets. Only one batch is affected (lot number 80623/1), and a recall for this batch has been initiated.

Advice for for clinical staff:

- Identify and isolate devices with this lot number
- Do not use them
- Contact the manufacturer to arrange for return and replacement

For further information see http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON036151

Stop press *cont.*

Effects of MRI on implantable drug pumps

In December 2008, we issued a medical device alert about MRI scanning of patients with implanted **Medtronic SynchroMed drug pumps**. These pumps provide baclofen and morphine therapy, but they do not behave as expected when exposed to the magnetic field of an MRI scan. Product labelling states that MRI temporarily stops the pump rotor and suspends drug infusion during MRI exposure. The pump should resume normal function when removed from the MRI field. However, we are aware of risks, including delays in drug infusion, after MRI of patients implanted with these devices.

Advice for healthcare professionals:

- Ensure that departmental procedures are in place for MRI scanning of patients with Medtronic SynchroMed implantable drug pumps
- When consultation with clinical and technical staff involved in the long-term management of the pump and patient has not been possible, consider:
  - Alternative imaging techniques if appropriate
  - More regular observations of the patient until confirmation that the pump has restarted
  - Contacting the manufacturer for advice if in doubt about pump status
  - Reporting drug-pump incidents to the manufacturer and the MHRA

See http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON033658

Oral bowel cleansing solutions: risk of harm

The National Patient Safety Agency has issued a Rapid Response Report on the risks of harm from use of **oral bowel cleansing solutions** (Picolax, Citrafleet, Fleet Phospho-Soda, Klean Prep, and Moviprep) before surgery or investigative procedures. Read the NPSA's report at http://www.npsa.nhs.uk/nrls/alerts-and-directives/rapidrr/reducing-risk-of-harm-from-oral-bowel-cleansing-solutions/

Other information from the MHRA

Patient Information Leaflets of the month: smoking-cessation aids

Access PIL of the month at http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleaflets andpackaging/Patientinformationleaflet(PIL) ofthemonth/index.htm

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this new initiative, we are publishing a series of examples of best practice on our website. To promote this new initiative, we are publishing a series of examples of best practice on our website. To coincide with National No Smoking Day on March 11, we are featuring the leaflets for medicines used in **smoking-cessation programmes**.

Consultation: changes to legislation and working during an influenza pandemic

For further information see http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON038669

Complete an online response form by visiting this link, or email Part3@mhra.gsi.gov.uk

In conjunction with the Department of Health and Home Office, we have issued proposals to change the legislation and working procedures during an influenza pandemic. We are seeking views on the manufacture, distribution, sale, and supply of medicines and devices during such a pandemic.

The consultation closes on March 20, 2009.

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines

Sign up to receive an email alert when a new issue is published: email registration@mhradrugsafety.org.uk

Report a suspected adverse drug reaction at www.yellowcard.gov.uk