

WHO PHARMACEUTICALS NEWSLETTER



World Health
Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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News & Issues

This issue covers regulatory and safety information on more than thirty medicines, both old and new products. Previous warnings have been reiterated, labels updated, products withdrawn or new adverse reaction reports have been recorded, as may be the case. The feature item includes recommendations from the fourth Meeting of the WHO Advisory Committee on Safety of Medicinal Products.

In the last issue we promised to include letters from you on items that we publish in our newsletters. We are happy to bring you one such letter on a feature article from 2006. By sharing this interesting exchange we hope that we can motivate you to take a more interactive interest. We look forward to receiving your comments on any items published in this newsletter.

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Letters to the WHO Pharmaceuticals Newsletter

Aprotinin

Label updated for specific use, new safety information

Canada. Health Canada has issued a Notice to Hospitals and a Public Communication with the following information:

- Aprotinin injection is indicated for prophylactic use to reduce blood loss and the need for blood transfusion only in those patients who have an increased risk of blood loss and blood transfusion associated with cardiopulmonary bypass during coronary artery bypass grafting.
- Administration of aprotinin increases the risk of renal dysfunction, and may increase the requirement for dialysis peri-operatively. The risk is particularly high in patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function.
- Aprotinin administration may cause fatal and nonfatal anaphylactic or anaphylactoid reactions, both with an initial (test) dose as well as with any of the components of the dose regimen. Fatal reactions have also occurred in situations where the initial (test) dose was tolerated. As a result, aprotinin should only be administered in operative settings where cardiopulmonary bypass can be rapidly initiated.
- The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure, and a history of any prior aprotinin exposure must be verified before aprotinin administration. The risk for a fatal reaction appears to be greater upon re-exposure within 12 months of the most recent prior aprotinin exposure. As a result the administration of aprotinin to patients with a known or suspected previous aprotinin

exposure during the last 12 months is contraindicated.

In the US the product label for aprotinin (Trasylol) has been revised to include a more focused indication for its use, and the above safety warnings and contraindications (see WHO Pharmaceuticals Newsletter No. 1, 2007).

References:

1. *Notice to Hospitals.* Health Canada, 27 March 2006 (www.hc-sc.gc.ca).
2. *Public Communication.* Health Canada, 27 March 2006 (www.hc-sc.gc.ca).

Attention deficit hyperactivity disorder (ADHD)-

treatments

Patients to be notified of cardiovascular and psychiatric events

USA. The United States Food and Drug Administration (US FDA) has issued a directive that patients receiving pharmacotherapies for attention-deficit hyperactivity disorder (ADHD) must be informed of potential cardiovascular and psychiatric adverse events by the manufacturers of such drug products. Manufacturers of ADHD therapies must develop Patient Medication Guides highlighting these possible risks and advise patients of precautions that can be taken. A US FDA review of ADHD products found reports of sudden death in patients with existing heart problems and reports of stroke and cardiac arrest in adults with certain risk factors. A second US FDA review identified a slight increase in the risk of ADHD drug-related psychiatric events such as auditory hallucinations, paranoid disorders and mania.

Reference:

FDA News. U.S. Food and Drug Administration, 21 February 2007 (www.fda.gov).

Drug-eluting stents

To be used with utmost restraint

Sweden. The Swedish Medical Products Agency (MPA), in conjunction with the National Board of Health and Welfare and the Swedish Society of Cardiology, has recommended utmost restraint in the use of drug-eluting stents. The recommendation was based on the results of clinical studies, including the Swedish Coronary and Angioplasty Registry (SCAAR) study that showed increased risk of thrombosis associated with the use of drug-eluting stents. The results of the SCAAR study and four other randomized studies showed that drug-eluting stents have no advantages in terms of myocardial infarction or mortality, compared with bare-metal stents; in addition, the SCAAR study data indicated a small, long-term increased risk of these events. According to the MPA, drug-eluting stents must only be used in patients for whom no other treatment alternative exists or in patients who are at greatly increased risk of restenosis and for whom the effect of restenosis is expected to be severe.

Reference:

Internet document. Swedish Medical Products Agency, 13 February 2007 (www.lakemedelsverket.se).

Interferon-1b

Not approved for idiopathic pulmonary fibrosis

USA. The US FDA has issued a Public Health Advisory about the early termination of the INSPIRE clinical study

(International Study of Survival Outcome in Idiopathic Pulmonary Fibrosis) of interferon- γ -1b (IFN- γ -1b) for idiopathic pulmonary fibrosis (IPF); the Agency says that IFN- γ -1b (Actimmune) is not approved for the treatment of IPF. An interim analysis of the INSPIRE study showed that IFN- γ -1b recipients did not benefit from the drug compared with 12.7% deaths in the placebo group; 14.5% of patients died in the IFN- γ -1b group. An independent data monitoring committee subsequently recommended early termination of the trial. IFN- γ -1b-related side effects reported in the INSPIRE trial included neutropenia, constitutional symptoms, and possibly pneumonia. The US FDA has advised patients who are receiving IFN- γ -1b to consult their doctors about whether they should continue the treatment. The Agency has also advised doctors to discuss the results of the INSPIRE trial with their patients who are receiving IFN- γ -1b for IPF, and to carefully consider whether the treatment should be continued in such patients or not.

Reference:

Public Health Advisory. U.S. Food and Drug Administration, 9 March 2007 (www.fda.gov).

Isotretinoin Web page about dangers of online buying

USA. The US FDA notified consumers and health-care professionals of a special web page launched to warn about the dangers of buying isotretinoin online. Isotretinoin is a drug approved for the treatment of severe acne that does not respond to other forms of treatment. If the drug is improperly used, it can cause severe side effects, including birth defects. Serious mental health problems have also been reported with isotretinoin use. The new web page, www.fda.gov/buyonline/accutane, will appear in online search results for one of the brand names of isotretinoin

(Accutane, Amnesteem, Claravis and Sotret). The web page warns that the drug should only be taken under the close supervision of a physician or a pharmacist, and provides links to helpful information. The new web page is in addition to special safeguards put in place by the US FDA and manufacturers of isotretinoin to reduce the risks of the drug, including a risk management programme called iPLEDGE. The aim of iPLEDGE is to ensure that women using isotretinoin do not become pregnant, and that women who are pregnant do not use isotretinoin.

Reference:

FDA Warning: Risks of buying Accutane (isotretinoin) over the Internet. U.S Food and Drug Administration, 28 March 2007 (www.fda.gov).

Metoclopramide Increasing reports of extrapyramidal symptoms in children; paediatric use tightened

The Netherlands. Following an increase in the number of registered cases of extrapyramidal symptoms in children receiving metoclopramide, the Medicines Evaluation Board (MEB) in the Netherlands has restricted the use of metoclopramide in this population. The Board says metoclopramide should be used only in the treatment of severe nausea and vomiting of known origin, and only if treatment with other products is ineffective or is not possible. The MEB says there are better alternatives to metoclopramide. For example, domperidone is a better choice in treating post-operative nausea in children. Domperidone is also the drug of choice in treating migraines in children because the risk of extrapyramidal effects is lower than with metoclopramide. Similarly, 5-HT₃ receptor antagonists (e.g. ondansetron)

are the drugs of first choice in nausea due to strongly emetogenic chemotherapy because of better efficacy and fewer adverse events than with metoclopramide.

Reference:

News and Publications. The Medicines Evaluation Board, the Netherlands, 21 February 2007 (www.cbg-meb.nl/uk/nieuws).

'First-in-man' clinical trials guideline for Public Consultation

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adapted a draft guideline for first-in-man clinical trials for potential high-risk medicinal products. This guideline has been prepared as one of the measures for minimizing the risk of serious adverse reactions of the nature that occurred during the first-in-man clinical trials of TGN1412. It gives guidance on managing the transition from non-clinical studies to first tests in humans for high-risk medicinal products.

The draft guideline has been released for a two-month public consultation. Comments are invited by 23 May 2007 (see www.emea.europa.eu for details).

Reference:

Press Release. EMEA, 26 March 2007.

Miconazole Interaction with warfarin

Finland. The use of miconazole (Daktarin) oral gel in patients receiving warfarin may lead to increased International Normalized Ratio (INR) for prothrombin time, warns Finland's National Agency for Medicines (NAM). Two cases

reported to NAM's adverse reaction database in 2005 were associated with the use of warfarin (Marevan) for auricular fibrillation and miconazole (Daktarin) oral gel. In the first, a 75-year-old woman receiving warfarin (Marevan) started treatment with miconazole (Daktarin) for an intestinal mycosis and, six days later, her INR increased from a therapeutic level to 15. In the second case, a 62-year-old woman receiving warfarin (Marevan) had a high (undetermined) INR level approximately two weeks after starting the miconazole gel (Daktarin) for candidiasis. In 2006, NAM received another report in which an 84-year-old woman, who was receiving warfarin (Marevan), developed haematuria and an increase in INR to >7 after starting treatment with the miconazole (Daktarin) oral gel. None of the patients developed serious haemorrhage and their INR levels normalized after miconazole gel was stopped and treatment was given (fresh frozen plasma, vitamin K and coagulation factor concentrate). In addition to the above cases, the national adverse reactions database has 10 non-fatal reports of interactions between warfarin (Marevan) and the miconazole (Daktarin) oral gel; all involve the potentiation of the effect of warfarin (Marevan) and some are associated with haemorrhage. NAM suggests that patients receiving warfarin should avoid the use of miconazole oral gel (Daktarin), and if alternative treatments are unavailable, INR levels should be checked frequently.

Reference:

TABU: Drug Information from the National Agency for Medicines, Finland, No. 6, 2006.

Omalizumab Label update about anaphylaxis

USA. The US FDA has asked Genentech to add a boxed warning to the labelling for omalizumab (Xolair) to warn

about possible anaphylaxis associated with the use of the drug. Anaphylaxis may include chest tightness, dizziness, pruritus, swelling of the mouth, syncope, trouble breathing and urticaria. The Agency has also requested Genentech to provide a patients 'Medication Guide' to strengthen the existing warning for anaphylaxis in the omalizumab (Xolair) label. According to the US FDA, the frequency of anaphylaxis reported in the clinical trials of omalizumab (Xolair) was about 0.1%, but the life-threatening potential and frequency of reports in the post-marketing experience of omalizumab (Xolair), and the possibility for the delayed anaphylaxis onset, have prompted the agency to recommend the boxed warning and strengthen the existing warning. The warning includes the possibility of developing anaphylaxis after any dose of omalizumab (Xolair); the anaphylaxis may be delayed up to 24 hours after administration. The US FDA has advised health-care providers to observe patients for at least two hours after an injection of omalizumab (Xolair).

Reports in WHO database:
Omalizumab (Xolair) -
Anaphylactic reaction - 28

Reference:

FDA News. U.S. Food and Drug Administration, 21 February 2007 (www.fda.gov).

Pentavalent rotavirus (W179- 9) vaccine Label updated with information on intussusceptions and haematochezia

USA. The US FDA is notifying health-care providers and the public about 28 post-marketing reports of intussusception following the administration of live, oral, pentavalent rotavirus

W179-9 vaccine (RotaTeq). Intussusception is a serious and potentially life-threatening condition that occurs when the intestine gets blocked or twisted. RotaTeq is indicated for the prevention of rotavirus gastroenteritis. It is not known how many of the 28 cases are vaccine-related and how many may have occurred by coincidence. The US Vaccine Adverse Event Reporting System (VAERS) received these reports between 3 February 2006 (when RotaTeq was licensed for use in the US) and 31 January 2007. Intussusception occurred after dose 1, dose 2 and dose 3 of the vaccine, and approximately 50% of cases occurred 1–21 days postvaccination (range 0–73 days). Surgical repair was necessary in 16 infants while the remaining infants had reduction of the intussusception by contrast or air enema.

The US FDA noted that the number of the rotavirus (W179-9) vaccine (RotaTeq)-associated intussusception cases reported to date does not exceed the expected number based on annual background rates of 8–43 cases per 100 000 for an unvaccinated population of infants aged 6–35 weeks. However, the agency acknowledged that vaccine adverse events are not always reported and that there may be additional unreported cases of intussusception following vaccination. Currently, there are two large-scale postmarketing studies being conducted by Merck & Co. (involving about 44 000 infants) and the US Centers for Disease Control and Prevention's Vaccine Safety Data Link (involving approximately 90 000 infants). The US prescribing information for rotavirus (W179-9) vaccine (RotaTeq) has been updated to reflect the above information.

Reference:

FDA Public Health Notification. U.S. Food and Drug Administration (Center for

Biologics Research and Evaluation), 13 February 2007 (www.fda.gov).

Methotrexate dosage errors

The Belgian Drug Monitoring Centre has received notification of two cases of severe adverse events resulting from dosage errors associated with methotrexate. In the first case, a patient misunderstood the dosage and took six 2.5 mg tablets of methotrexate a day for two weeks, instead of six tablets a week, for rheumatoid arthritis. In the second case, a patient took three 2.5 mg tablets of methotrexate a day for one week, instead of one tablet a day, for psoriasis, on a friend's advice. Both patients were hospitalized for diarrhoea and mucositis, and one developed pronounced bone marrow depletion.

The Belgian Drug Monitoring Centre says that confusion may arise when a drug does not have to be taken every day. Such errors have been reported with mefloquine for malaria prevention with, for example, one dose being taken daily instead of weekly. Unusual dosages are also seen with some bisphosphonates: weekly for risedronic acid (Actonel Hebdomadaire) and alendronic acid (Fosamax Hebdomadaire), and monthly for ibandronic acid.

The Centre suggests that patient reminders may be useful in the case of drugs with an unusual dosage, by providing a note and clearly specifying the dose on the drug container.

Reference:

Folia Pharmacotherapeutica 33(12): 108, 2006.

Pergolide

Risk of heart valve damage; to be removed from the market

USA (1). Manufacturers have volunteered to remove pergolide drug products from the market due to the risk of serious damage to the heart valves of patients treated with these products. Pergolide is a dopamine agonist and is used with levodopa and carbidopa to manage the symptoms of Parkinson's disease. The US FDA notes that new studies confirm old data associating pergolide with increased chance of regurgitation (back-flow of blood) of the mitral, tricuspid and aortic valves of the heart. Valve regurgitation is a condition in which valves do not close tightly, allowing blood to flow backward across the valve. Symptoms include shortness of breath, fatigue and heart palpitations. Valvular heart disease was first described in association with pergolide in 2002. In 2003 the product label was updated to include valvulopathy to the warnings section. Then in 2006, the warning was upgraded to a black box warning because of new data concerning risks of heart valve damage. The Agency advises that the products being removed include two generic versions of pergolide manufactured by Par and Teca and a proprietary version (Permax) manufactured by Valeant Pharmaceuticals. The removal of these products is not expected to adversely affect patient care because alternative therapies are available. The US FDA cautions that it is dangerous to stop taking the medication abruptly and that patients should consult their physicians to discuss switching to appropriate alternative medications. The US FDA is working with manufacturers of pergolide to determine if it might be possible, once the drug is withdrawn from the market, to make the drug available under

an Investigational New Drug (IND) application for those few patients who are currently receiving pergolide and who cannot be successfully switched to other available treatments.

Canada (2). Health Canada has informed that it is currently evaluating the new data on the risk of heart problems associated with pergolide treatment. When completed, results of the review will be communicated to the public and to health-care providers. Health Canada stresses that patients should not stop taking their medication without consulting their physician since sudden discontinuation of pergolide may have serious consequences for the patient.

References:

1. *FDA News*. U.S. Food and Drug Administration, 29 March 2007 (www.fda.gov).
2. *Information Update*. Health Canada, 31 March 2007 (www.hc-sc.gc.ca).

Pioglitazone

Fractures in females

USA. Takeda Pharmaceuticals and the US FDA notified health-care professionals of recent safety data concerning pioglitazone-containing products. The results of an analysis of the manufacturer's clinical trial database of pioglitazone showed more reports of fractures in female patients taking pioglitazone than those taking a comparator (either placebo or active). The majority of fractures observed in female patients were in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia). There were more than 8100 patients in the pioglitazone-treated groups and over 7400 patients in the comparator-treated groups. The duration of pioglitazone treatment was up to 3.5 years. The US FDA advises that health-care professionals should consider the risk of

fracture when initiating or treating female type 2 diabetes mellitus patients with pioglitazone-containing products.

Reference:

'Dear Health-care Provider' letter from Takeda Pharmaceuticals, March 2007 (www.fda.gov).

Sedative-hypnotic drugs

Stronger warnings about allergic reactions and sleep-related complex behaviours.

USA. The US FDA has requested a labelling change for all sedative-hypnotic drug products to include a stronger warning of potential risks such as severe allergic reactions and complex sleep-related behaviours. The manufacturers of sedative-hypnotic drugs must revise product labelling to include warnings about anaphylaxis and angioedema, which can occur as early as first administration, and complex sleep related behaviours such as sleep-driving, making telephone calls and eating food while asleep. They must also alert health-care providers about these new warnings and develop Patient Medication Guides to inform patients about the risks and potential precautions that can be taken. Since there may be differences among the various sedative-hypnotic drugs, the US FDA has recommended that the manufacturers conduct clinical trials to assess the frequency of sleep-related behaviours for individual products. Zolpidem (Ambien), flurazepam (Dalmene), triazolam (Halcion), ethchlorvynol (Placidyl), secobarbital (Seconal), zaleplon (Sonata) are some of the medicines that are the focus of the revised labelling.

Reference:

FDA News. U.S. Food and Drug Administration, 14 March 2007 (www.fda.gov).

Tegaserod Withdrawn due to life-threatening cardiac effects

USA. Novartis Pharmaceuticals Corporation in consultation with the US FDA has agreed to withdraw tegaserod from the market. This measure follows a new safety analysis that has found a higher chance of heart attack, stroke, and worsening of chest pain in patients treated with tegaserod maleate (Zelnorm) compared to those treated with a placebo.

Tegaserod is a prescription medication approved for short-term treatment of women with irritable bowel syndrome with constipation and for patients under 65 years of age with chronic constipation. The US FDA has analysed the results of 29 clinical studies of tegaserod (Zelnorm) for the treatment of a variety of gastrointestinal tract conditions. These 29 studies included 11 614 patients treated with tegaserod maleate and 7031 treated with a sugar pill. The average age of these patients was 43 years and 88% were women. The number of patients who suffered a heart attack, stroke or severe chest pain that can turn into a heart attack was small. However, patients treated with tegaserod maleate had a higher chance of having any of these serious and life-threatening side effects than did those on the sugar pill. Thirteen patients (0.1%) treated with tegaserod maleate had serious and life-threatening cardiovascular side effects. Among these, four had a heart attack (one died), six had a type of severe chest pain which can quickly turn into a heart attack and three had a stroke. Among the patients taking the sugar pill, only one (or 0.01%) had symptoms suggesting the beginning of a stroke that resolved without complication. The Agency will work with Novartis to allow special access to tegaserod maleate (Zelnorm) for those patients for whom no

other treatment options are available and in whom the benefits outweigh the chance of serious adverse effects.

Reference:

FDA Public Health Advisory. U.S. Food and Drug Administration, 30 March 2007 (www.fda.gov).

Telithromycin Updates on use, contraindications, adverse events

USA (1). The US FDA has finalized revisions to the telithromycin (Ketek) label, which include removing two of the three previously approved indications – acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis. The Agency determined that the balance of benefits and risks no longer supported approval of telithromycin (Ketek) in the two indications. The antibacterial will remain on the market for the treatment of community-acquired pneumonia of mild-to-moderate severity. Additional changes include a boxed warning that telithromycin is contraindicated in patients with myasthenia gravis and a strengthened warning section regarding specific drug-related adverse events including visual disturbances and loss of consciousness.

Europe (2). The European Medicines Agency (EMA) has recommended restrictions on the use of telithromycin (Ketek) in three of its four approved indications: for the treatment of bronchitis, sinusitis and tonsillitis/pharyngitis; telithromycin should only be used for infections caused by bacterial strains that are suspected or proven to be resistant to or cannot be treated with macrolide or beta-lactam antibiotics. The Agency has recommended no restrictions for the remaining indication, the treatment of community-acquired

pneumonia. The Agency has also recommended the contraindication of the use of telithromycin in patients with myasthenia gravis and strengthened warnings on transient loss of consciousness and effects on vision. These recommendations are based on the conclusions of a comprehensive review that the Agency has been carrying out since January 2006, following reports of severe liver injuries in patients taking telithromycin.

References:

1. *Press Release. U.S. Food and Drug Administration, 12 February 2007 (www.fda.gov).*
2. *Press Release. European Medicines Agency, 30 March 2007 (www.emea.europa.eu).*

Topical anaesthetics

Professional advice needed before use in cosmetic procedures

USA. The US FDA has issued a Public Health Advisory about life-threatening adverse effects associated with topical anaesthetics for cosmetic procedures. These products contain drugs such as benzocaine, lidocaine, prilocaine and tetracaine. The Agency is aware of two women who developed seizures and went into a coma and subsequently died after applying topical anaesthetics before laser hair removal; these creams, which were made in pharmacies, contained high amounts of lidocaine and tetracaine. The Agency has also received reports of serious and life-threatening adverse effects such as coma, irregular heart beat and seizures associated with these products. Those who are thinking about a cosmetic or medical procedure on the skin are advised to discuss with their doctor whether they need a topical anaesthetic and, if so, to use a product approved by the US FDA.

Reference:

FDA Public Health Advisory. U.S. Food and Drug Administration, 6 February 2007 (www.fda.gov).

Heparin: Medication Errors

There is a potential for life-threatening medication errors with two heparin preparations, advise Baxter in a 'Dear Health-care Provider' letter posted on the US FDA website. The two products involved are heparin sodium injection 10 000 units/mL and Hep-Lock U/P 10 units/mL, which have similar colour labelling. Baxter are aware of fatal medication errors occurring when one product has been mistaken for another, including three infant deaths following inadvertent administration of heparin 10 000 units/mL instead of Hep-Lock 10 units/mL. Baxter advise that health-care professionals should carefully read the product label and should not rely solely on label colour to distinguish between products.

Reference:

'Dear Health-care Provider' letter from Baxter Healthcare Corporation, 6 February 2007 (www.fda.gov).

Angiotensin Converting Enzyme (ACE) inhibitors

Reports of visual disturbances

The Netherlands. Until 24 March 2006, the Netherlands Pharmacovigilance Centre, Lareb had received six reports of visual hallucinations associated with the use of ACE inhibitors. Lareb advises that these included two reports with lisinopril and one report each with captopril, enalapril, ramipril and trandolapril. According to Lareb, there was complete recovery in all cases once the suspect drug was discontinued. Lareb suggests that the successful dechallenges support a causal relationship between the ACE inhibitors and the development of visual hallucinations.

Reference:

ACE inhibitors and hallucinations. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Antiepileptic drugs

Enzyme-inducing drugs may increase fracture risk

Australia. According to the Australian Adverse Drug Reactions Advisory Committee (ADRAC), decreased bone mineral density and a subsequent increased fracture risk have been documented in users of enzyme-inducing antiepileptic drugs such as phenobarbital, phenytoin and primidone. ADRAC says this risk increases with the duration of drug exposure and is higher in women; there is presently no information on the effect of 'new' antiepileptics on bone health, but this has not been

investigated in appropriate studies. ADRAC has received relatively few reports of decreased bone mineral density associated with antiepileptic drugs, but notes that this may reflect a low level of awareness of this adverse effect and the delayed nature of the events, which often manifest years after treatment initiation.

Reference:

Australian Adverse Drug Reactions Bulletin 26(1): 3, 2007.

Antipsychotics

Reports of neuroleptic malignant syndrome

Australia. Previously (1997 and 1999) ADRAC had noted that two of the oldest atypical antipsychotics, clozapine and olanzapine can cause neuroleptic malignant syndrome (NMS). It now appears that all of the atypical antipsychotics available in Australia can cause this problem. In the Australian database there are 16 reports of NMS with quetiapine (this being 5.2 % of all reports received for this medicine), 45 for risperidone (5.7%), 15 for amisulpride (6.7 %), 15 for aripiprazole (10.3 %). There are in all 85 NMS reports for clozapine (2.3 %) and 49 for olanzapine (4.1 %) in the Australian database. Although with the Australian data it appears that, of the atypical antipsychotics, NMS occurs most with aripiprazole, this trend is not seen in the WHO global database. Clinical features of NMS include autonomic instability, confusion, disorientation or other cognitive function changes, fever, muscle rigidity and profuse sweating. Increased creatine kinase (CK) is often noted. ADRAC advises that NMS can be life-threatening and rapid recognition and treatment are important.

Reports in WHO database:

Amisulpride - 73
Aripiprazole - 115
Quetiapine - 33
Risperidone - 684

Reference:

Australian Adverse Drug Reactions Bulletin 26(2): 2, 2007.

Bupropion

Reports of depression

The Netherlands. Until 1 March 2006 Lareb had received 37 reports of depression associated with bupropion (amfebutamone; Zyban). Of these reports, 15 were explicitly associated with suicidality, including attempted suicide. The 15 patients ranged in age from 31–80 years and, following the start of bupropion treatment, 10 patients developed suicidal tendencies, two patients developed thoughts of self-harm, two patients developed suicidal ideation and one patient attempted suicide; there was a latency of three days to 11 weeks. In eight patients there was a positive dechallenge and in four there was a negative dechallenge; information regarding dechallenge was unknown in two patients.

Reports in WHO database:

Depression - 1345
Suicide attempts - 1161

Reference:

Bupropion and suicidality. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Carbasalate

Reports of tinnitus

The Netherlands. There are eight reports of tinnitus associated with carbasalate calcium at doses of 38 mg and 100 mg in the Lareb database. Carbasalate calcium is used in the treatment of fever, headache and pain due to 'flu and in other conditions like

myalgia. The drug was administered once daily in all of the reports involving the 38 mg dose. Lareb also received two reports of tinnitus associated with carbasalate calcium 600 mg, one report of ototoxicity associated with 38 mg, and one report of decreased hearing with 300 mg. The range of the time to reaction (onset) was broad, and, at the time of reporting, two of the patients had not recovered after withdrawal of the drug.

According to Lareb, although the mechanism of the treatment induced ototoxicity is not apparent, it "may involve biochemical and consequent electrophysiological changes in the inner ear and a dysfunction of the auditory nerve". Lareb concludes that the association between tinnitus and the lower doses (38 and 100 mg) is disproportionate in the Lareb database, and that their data suggest an association between tinnitus and low doses of carbasalate calcium.

Reports in WHO database:
Tinnitus - 7

Reference:

Low dose carbasalate calcium and tinnitus. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Codeine

Lowest dose recommended in nursing mothers

Sweden. The Swedish Medical Products Agency (MPA) has warned that, in rare cases, codeine in normal doses given to breastfeeding mothers can lead to dangerously high amounts of morphine being delivered to the infant. Codeine is converted to morphine in the body, and mothers who are ultra-rapid metabolizers of codeine should be aware of possible signs of morphine overdose in their infants. In a case reported in Canada, an infant died after receiving high

doses of morphine through breast milk. The mother was an ultra-rapid metabolizer receiving analgesia with codeine for pain resulting from the delivery. The Swedish MPA warns that breastfeeding mothers receiving codeine should use the lowest dose possible and monitor their infant for signs of overdose such as breathing difficulties, difficulty breastfeeding, drowsiness or listlessness, flaccidity and small pupils; should any of these signs be noted, medical care should immediately be sought.

Reference:

Codeine in normal doses to breastfeeding mothers can in rare cases cause serious adverse reactions in the infant. Internet Document. Swedish Medical Products Agency, December 2006 (www.lakemedelsverket.se).

Deferasirox

Reports of renal failure

Canada, Switzerland.

Novartis Pharma has issued a 'Dear Health-care Professional' letter advising of a possible association between the use of deferasirox (Exjade) and renal failure and cytopenia. Deferasirox is an iron-chelator. According to Novartis, reports of renal failure have been received following the post-marketing use of deferasirox (Exjade). Some of these reports had a fatal outcome. The fatalities could have been because of the underlying diseases. However, the company says that it is impossible to rule out a contributory role of deferasirox (Exjade). Discontinuation of deferasirox (Exjade) in most of the nonfatal cases was associated with improvement in patients' condition, which is suggestive of a contributory role of deferasirox (Exjade). Clinical trials have revealed dose-dependent increases in serum creatinine levels in patients receiving deferasirox

(Exjade). Increases in creatinine levels occurred at a greater frequency in deferasirox recipients, compared with deferoxamine (another iron-chelator) recipients. The company says that serum creatinine levels should be monitored twice before initiating deferasirox (Exjade), followed by weekly monitoring in the first month of treatment, and monthly thereafter; proteinuria should be monitored every month and patients should be adequately hydrated. Novartis has also received reports of cytopenia in patients receiving deferasirox (Exjade), most of whom had pre-existing haematological disorders. In line with standard clinical management of cytopenias, blood counts should be monitored regularly. Interruption of treatment with deferasirox should be considered in patients who develop unexplained cytopenia.

References:

1. 'Dear Health-care Professional' letter from Novartis Pharmaceuticals Canada Inc., 9 March 2007 (www.hc-sc.gc.ca).
2. 'Dear Doctor' letter from Novartis Pharma Schweiz AG, 28 March 2007 (www.swissmedic.ch).

Domperidone

Heart rate and rhythm disorders

Canada. From 1 January 1985 to 15 August 2006, Health Canada received nine domestic reports of heart rate and rhythm disorders suspected of being linked with domperidone use. Four of these reports described torsades de pointes and two described QT interval prolongation. The other three reports included the following adverse reactions: arrhythmia, atrial fibrillation, bradycardia, palpitation and ventricular tachycardia. Five patients had recovered at the time of reporting and the outcome was not known in the remaining four

cases. The reports involved patients aged from two months to 74 years.

Reports in the WHO database: Heart rate and rhythm disorders - 62

Reference:

Canadian Adverse Reaction Newsletter, January 2007, 17(1): 2.

Entecavir Report of a resistant HIV-variant in HIV/HBV co-infected patient

Canada, Europe. Bristol-Myers Squibb in consultation with Health Canada (1) and Swissmedic (2) has written to health professionals with the following warning about the use of entecavir (Baraclude):

- Entecavir (Baraclude) has not been assessed in HIV/HBV (hepatitis B) co-infected patients who are not simultaneously receiving effective HIV treatment.
- When considering therapy with entecavir (Baraclude) in an HIV/HBV co-infected patient who is not receiving HAART, the risk of developing HIV resistance cannot be excluded based on current information.
- Caution is advised if entecavir (Baraclude) is used in this setting.

The EMEA has also made a Public Statement (3) with similar information.

The above warning was issued because an HIV variant containing the M184 resistance substitution was documented during entecavir (Baraclude) treatment in an HIV/HBV co-infected patient who was not simultaneously receiving HAART.

Reports in WHO database: Entecavir (Baraclude) HIV test positive - 1

References:

1. *Advisory. Health Canada, 21 February 2007 (www.hc-sc.gc.ca).*
2. *'Dear Doctor' letter from Bristol-Myers Squibb SA, March 2007 (www.swissmedic.ch).*
3. *Public Statement. European Medicines Agency, 5 March 2007 (www.emea.eu.int).*

Erythropoiesis- stimulating agents

New studies suggest serious and life- threatening side effects

USA. The US FDA is warning health-care professionals and the public of new safety information for erythropoiesis-stimulating agents (ESAs) darbepoetin alfa (Aranesp) and epoetin alfa (Epogen and Procrit). ESAs are genetically engineered forms of the naturally occurring human protein, erythropoietin. ESAs stimulate the bone marrow to make more red blood cells and are the US FDA approved for use in reducing the need for blood transfusions in patients with chronic kidney failure, cancer patients on chemotherapy, patients scheduled for major surgery (except heart surgery) and patients with HIV who are using AZT. Four new studies in patients with cancer found a higher chance of serious and life-threatening side effects or death with the use of ESAs. These research studies were either evaluating an unapproved dosing regimen, a patient population for which ESAs are not approved, or a new unapproved ESA.

The US FDA has issued a Public Health Advisory with the following information:

- A higher chance of death and an increased rate of tumour growth were reported in patients with

advanced head and neck cancer receiving radiation therapy and in patients with metastatic breast cancer receiving chemotherapy, when ESAs were given to maintain haemoglobin levels of more than 12 g/dL.

- A higher chance of death was reported and no fewer blood transfusions were received when ESAs were given to patients with cancer and anaemia not receiving chemotherapy.
- A higher chance of death was reported and an increased number of blood clots, heart attacks, heart failure and strokes were reported in patients with chronic kidney failure when ESAs were given to maintain haemoglobin levels of more than 12 g/dL.
- A higher chance of blood clots was reported in patients who were scheduled for major surgery and given ESAs.
- ESAs are not approved for treatment of the symptoms of anaemia such as fatigue in patients with cancer, surgical patients and patients with HIV.

The US FDA believes these new concerns apply to all ESAs and is re-evaluating how to safely use this product class. The US FDA and Amgen, (the manufacturer of Aranesp, Epogen and Procrit), have changed the full prescribing information for these drugs to include a new boxed warning, updated warnings, and a change to the dosage and administration sections for all ESAs. The new boxed warning advises physicians to monitor red blood cell levels (haemoglobin) and to adjust the ESA dose to maintain the lowest haemoglobin level needed to avoid the need for blood transfusions. The US FDA advises that physicians and patients should carefully weigh the risks of ESAs against transfusion risks.

(See WHO Pharmaceuticals Newsletter No. 1, 2006 for earlier revision to the ESA product labelling).

References:

1. *FDA News. U.S. FDA, 9 March 2007* (www.fda.gov).
2. *Public Health Advisory. U.S. FDA, 9 March 2007* (www.fda.gov).

Estazolam Present in a dietary supplement

Canada. Health Canada has advised against using Sleepees, an herbal sleep aid, as it was found to contain undeclared estazolam. Estazolam can be habit-forming when used for as little as a few months. Health Canada has advised consumers, who still have Sleepees in their homes, to consult a health-care professional before discontinuing the drug as it may cause withdrawal symptoms. Estazolam should not be used by individuals who are allergic to benzodiazepines, or those with myasthenia gravis or sleep-apnoea syndrome. Pregnant women should receive estazolam only when absolutely necessary and caution is needed when using the drug in the elderly or in those with a history of substance abuse, says the Agency. The side effects associated with estazolam use include amnesia, confusion, depression, dizziness, drowsiness and hallucinations. According to Health Canada, Sleepees is not authorized for sale in Canada and consumers who have purchased the product should return it to the place of purchase.

Reports associated with estazolam in WHO database:

- Tolerance increased - 11
- Therapeutic response decreased - 14
- Death - 14
- Nausea - 13
- Confusion - 9
- Hallucinations - 10
- Amnesia - 8
- Somnolence - 22

Dreaming abnormal - 19
Insomnia - 17

Reference:

Advisory. Health Canada, 23 February 2007 (www.hc-sc.gc.ca).

Fluticasone Reports of behavioural changes

The Netherlands. Lareb has received 17 reports of behavioural changes in children associated with the use of inhaled fluticasone propionate (n = 13) or salmeterol/fluticasone propionate (4). According to Lareb, in 11 cases, symptoms disappeared when fluticasone propionate was withdrawn. A positive rechallenge was observed in one case. Lareb states that six patients who had received fluticasone propionate also received salbutamol; however, in all but one case, the reporter did not see a causal relationship between the adverse drug reaction and salbutamol. These results, say Lareb, support "our theory that fluticasone is responsible for the behavioural changes in the children." Lareb says that psychiatric effects have also been reported in association with the use of oral corticosteroids and inhaled budesonide, which raises the possibility of a group effect.

Reference:

Fluticasone inhalation and behavioural changes in children. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Goserelin, buserelin Reports of psychiatric disorders

The Netherlands. Lareb has received five reports of psychiatric disorders associated with use of goserelin (n = 4) or buserelin (1) in men (aged 56–80 years). There were no

reports of psychiatric disorders associated with leuprorelin. The time to reaction onset was seven months for the buserelin recipient and one week to five months for three of the goserelin recipients; the time to reaction onset was not reported for one of the goserelin recipients. Reported adverse reactions included depression, emotional lability, insomnia, psychosis and sleep disorder. Only one patient had a history of a psychiatric disorder. Two patients received treatment with antipsychotics or antidepressants. The reported outcome was 'recovered' for two patients and 'not recovered' for two patients; the patient outcome for the remaining patient was not reported.

Reports in WHO database:
Goserelin, Psychiatric disorder - 222;
Buserelin, Psychiatric disorder - 84;
Leuprorelin, Psychiatric disorder - 799

Reference:

Goserelin and psychiatric disorders in the treatment of prostate cancer. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Levofloxacin Reports of blood glucose, liver and biliary disorders: an update

Canada. Between 1 January 1997 and 30 June 2006, Health Canada received 22 reports of dysglycaemia and 44 reports of liver and biliary disorders suspected to be associated with levofloxacin. The reports of dysglycaemia included diabetes mellitus (1 report), hyperglycaemia (2), hypoglycaemia (16), and combined hyper- and hypoglycaemia; the median reported age was 71 years. The 44 reports of levofloxacin-related liver and biliary disorders included 15 reports of

liver failure, hepatitis and hepato-renal syndrome, of which five reports had fatal outcomes; the remaining 29 reports included elevated liver enzyme levels, jaundice and cholestatic hepatitis. For all reports of liver and biliary disorders, the median time to onset was five days. The disturbances of blood glucose levels along with liver and biliary disorders are included in the product monograph of levofloxacin.

Reports associated with levofloxacin in WHO database:
Hepatic function abnormal - 111

Reference:

Canadian Adverse Reaction Newsletter, January 2007, 17(1): 1-2.

Linezolid

Risk of death when used in catheter-related blood stream infections

USA. The US FDA has issued an alert advising that the use of linezolid to treat seriously ill patients with intravenous catheter-related bloodstream infections may be associated with an increased risk of death. This alert follows data from an open-label, randomized trial that compared linezolid to vancomycin, oxacillin, or dicloxacillin (comparator antibiotics) in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections including those with catheter-site infections. Patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Patients with Gram-positive infections had no difference in mortality according to their antibiotic treatment. In contrast, mortality was higher in patients treated with linezolid who were infected with Gram-negative organisms alone, with both

Gram-positive and Gram-negative organisms, or who had no infection when they entered the study.

The US FDA reminds health-care professionals that linezolid is not approved for the treatment of catheter-related bloodstream infections, catheter-site infections or Gram-negative infections. If infection with Gram-negative bacteria is known or suspected, appropriate therapy should be started immediately. The US FDA is currently evaluating the new study along with other information about linezolid.

Reports in WHO database:
Death - 12

Reference:

FDA News. U.S. Food and Drug Administration, 16 March 2007 (www.fda.gov).

Olanzapine

Reports of amenorrhoea

The Netherlands. As recorded on 27 April 2006, there are seven reports of amenorrhoea associated with the use of olanzapine in the Lareb database. The time to reaction onset ranged from a few weeks to 10 months, and the patient outcome was reported in three cases; one patient recovered after the drug was discontinued, and two patients did not recover. Furthermore, four of the seven patients were concomitantly receiving a benzodiazepine, and one patient also experienced hyperprolactinaemia.

Reports in WHO database:
Amenorrhoea - 54

Reference:

Olanzapine and amenorrhoea. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Oseltamivir

Close monitoring of treated children and adolescents.

Japan (1). The Ministry of Health, Labour and Welfare in Japan has issued a general warning for oseltamivir (Tamiflu) advising close monitoring (for at least two days after diagnosis) of children and adolescents with 'flu who are receiving the drug. The warning follows the recent reports of two teenagers receiving oseltamivir who fell from buildings and died. In total, 16 deaths in oseltamivir recipients aged <16 years had been reported in Japan by October 2006, several involving falls from high places.

Europe (2). In a Press Release the European Medicines Agency (EMA) states that it is aware of the new reports of neuropsychiatric adverse events associated with the use of oseltamivir (Tamiflu) in Japan. The Agency's Committee for Medicinal Products for Human use (CHMP) has monitored closely all adverse drug reactions reported in connection with the use of oseltamivir since it was introduced in the European Union in 2003. In February 2007 the CHMP recommended an update of the product information to warn health professionals and patients about neuropsychiatric side effects with oseltamivir. According to the CHMP 'Patients, especially children and adolescents should be closely monitored and their health-care professional should be contacted immediately if the patient shows any sign of unusual behaviour'. The EMA and the CHMP will continue to closely monitor any emerging safety information on oseltamivir (Tamiflu), including neuropsychiatric disorders and will take further action if needed.

(See WHO Pharmaceuticals Newsletter No. 6, 2006 for

oseltamivir label updates in Canada and in the USA).

Reports in WHO database:
Oseltamivir (Tamiflu) - suicide attempts - 3

References:

1. *Adis Reactions (Weekly) No. 1143: 2, 2007.*
2. *Press Release. European Medicines Agency (EMA), 23 March 2007 (www.emea.europa.eu).*

Quetiapine Reports of alopecia

New Zealand. The Intensive Medicines Monitoring Programme (IMMP) has received two reports of alopecia associated with quetiapine. The first case reported to the IMMP involved a 34-year-old woman with psychotic depression. Approximately six weeks after starting therapy with citalopram and quetiapine (initially 25 mg/day and titrated to 100 mg/day), she noticed significant, continuing hair loss. Quetiapine was withdrawn one week later and her alopecia resolved; citalopram was continued throughout. The second patient was a 34-year-old woman with bipolar disorder who was receiving quetiapine 300 mg/day, zopiclone and clonazepam; she was also using a salbutamol (Albuterol) inhaler as required. She developed increasing hair loss 20 days after starting quetiapine; her medical history recorded alopecia while receiving valproic acid. Quetiapine was stopped and her hair loss resolved.

According to Dr McLean and Dr Harrison-Woolrych, the positive dechallenges and "the temporal relationship with the medicine in each case provides evidence of a 'probable' causal association".

Reports in WHO database:
Quetiapine - Alopecia - 22

Reference:

McLean RM, Harrison-Woolrych M. Alopecia associated with quetiapine. International Clinical Psychopharmacology No. 2, 2007, 22: 117-119.

Selective serotonin reuptake inhibitors (SSRIs), venlafaxine Reports of bruxism

The Netherlands. Lareb, the Pharmacovigilance Centre in the Netherlands has received seven reports of bruxism (teeth grinding) associated with SSRIs (two with citalopram, one with fluoxetine, one with fluvoxamine, three reports with paroxetine,) and three reports associated with venlafaxine use, up until 5 April 2006. The SSRI cases were reported at dosages of 20 mg/day for paroxetine, citalopram and fluoxetine, and 100 mg/day for fluvoxamine. The time to bruxism onset ranged from six hours to eight weeks, although the time to onset was not known in three SSRI cases. Recovery occurred in three cases following cessation of the SSRI, although one patient had permanent enamel damage; bruxism did not resolve in one patient and the outcome was unknown in three patients. The venlafaxine cases were reported at dosages of 75 mg/day. The time to bruxism onset ranged from days to weeks in two cases; the time to onset was unknown in one case. According to Lareb, bruxism was disproportionately associated with the use of SSRIs and venlafaxine in both the WHO and Lareb databases.

Reports in WHO database:
Citalopram - teeth grinding - 16
Fluoxetine - teeth grinding - 14
Fluvoxamine -teeth grinding - 1
Paroxetine - teeth grinding - 46

Venlafaxine - teeth grinding - 32

Reference:

SSRIs and venlafaxine in association with bruxism. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Ranibizumab Intravitreal injections and incidence of stroke

USA. Genentech has issued a 'Dear Health-care Provider' letter advising of important safety information regarding ranibizumab injection (Lucentis). The letter refers to interim data from the ongoing study which show that patients with neovascular (wet) age-related macular degeneration (AMD) who received intravitreal ranibizumab in doses of 0.5 mg had a significantly higher incidence of stroke compared with those patients in the 0.3 mg dose group (1.2% versus 0.3%). Patients with a prior stroke history appeared to be at greater risk for subsequent stroke. There was no difference between the doses for the events of myocardial infarction or vascular death.

Reference:

'Dear Health-care Provider' letter from Genentech, 24 January 2007 (www.fda.gov).

Rosiglitazone Increased risk of fractures in women receiving long-term treatment

USA (1), Canada (2), Switzerland (3), UK (4). According to a 'Dear Health-Care Professional' letter from GlaxoSmithKline, the ADOPT (A Diabetes Outcome and Progression Trial) safety data suggest an increased rate of fractures in women receiving rosiglitazone-containing products for type 2 diabetes. The information applies to rosiglitazone maleate

(Avandia), rosiglitazone maleate and metformin hydrochloride (Avandamet) and rosiglitazone maleate and glimepiride (Avandaryl). The primary goal of the ADOPT study was to compare the glycaemic control with rosiglitazone relative to metformin and to glibenclamide monotherapies in 4360 randomised patients with type 2 diabetes mellitus. While a review of the ADOPT safety data was generally consistent with the known safety profile of rosiglitazone, significantly more women receiving rosiglitazone experienced fractures (9.3%) than women receiving metformin or glibenclamide (5.1% and 3.5%, respectively). The incidence of fractures in men was similar for all three drugs. At the company's request, an independent safety committee conducted an interim analysis of safety data for another large, ongoing trial of rosiglitazone; the results of the preliminary analysis were consistent with the ADOPT findings. The independent safety committee recommended that the second trial continue without modification; final results should be available in 2009, according to GlaxoSmithKline.

Reports in WHO database:
Rosiglitazone - Fracture - 6
Fracture pathological - 1
Fracture spontaneous - 1

References:

1. 'Dear Health-care Provider' letter from GlaxoSmithKline, February 2007 (www.fda.gov).
2. 'Dear Health-care Professional' letter from GlaxoSmithKline, 23 February 2007 (www.hc-sc.gc.ca).
3. 'Dear Health-care Provider' letter from GlaxoSmithKline, 8 March 2007 (www.swissmedic.ch).
4. 'Dear Health-care Provider' letter from GlaxoSmithKline,

22 March 2007
(www.mhra.gov.uk).

Tacrolimus Reports of malignancies

The Netherlands. Lareb, the Pharmacovigilance Centre in the Netherlands has received three reports of malignant adverse effects associated with topical tacrolimus (Protopic) up to 6 June 2006. In all three cases, 0.03% tacrolimus (Protopic) was used. In one case, a child developed T-cell leukaemia two years after starting tacrolimus therapy and, at the time of notification, the child had not recovered. In the second case, a man developed a squamous cell carcinoma on the glans of his penis one year after starting tacrolimus therapy; the patient's outcome was unknown. In the third case, an elderly woman developed a malignant tumour of her tongue which required the surgical removal of a part of her tongue. Topical tacrolimus is used in atopic dermatitis. Lareb says that, because topical tacrolimus is often used for extended periods and off-label use is not uncommon, health professionals should be aware of a potential risk for malignancies.

Reports in WHO database:
Tacrolimus - Neoplasm - 206

Reference:

Topical tacrolimus and malignancies. Lareb, Netherlands Pharmacovigilance Centre, January 2007 (www.lareb.nl).

Zolpidem Reports of sleep walking

Australia. From the time when zolpidem (Stilnox) was marketed in Australia in late 2000 to the time of this report, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) had received

16 reports of sleep walking associated with its use; the reports detail inappropriate or strange autonomic behaviour while the individuals were 'asleep'. Among the reports were two cases involving uncontrollable eating binges during sleep. In the first report the patient's weight increased by 23 kg over seven months while receiving zolpidem. The problem of weight gain was resolved after the patient was found eating while asleep. The second report involved a patient who experienced significant weight gain with zolpidem therapy; again, the patient was discovered eating while asleep. The 16 reports also included one where a patient had been painting while asleep, and two reports which suggested the patients may have driven while asleep. Patients, and in particular first-time users, should be warned about the possibility of 'distressing' neurological or psychiatric reactions associated with zolpidem, including those associated with sleeping, according to ADRAC.

Reports in WHO database:
Zolpidem - Somnambulism - 66

Reference:

Australian Adverse Drug Reactions Bulletin 26 (1): 2-3, 2007.

Recommendations of the fourth meeting of the WHO Advisory Committee on Safety of Medicinal Products 26 and 27 February 2007

Constituted to provide advice on pharmacovigilance policy, and issues related to the safety and effectiveness of medicinal products, the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held its fourth meeting in February 2007. The following are the key recommendations from the meeting.

WHO Strategy for Medicine Safety

A strategy for safety of medicines in WHO is under preparation. A plan is needed for capacity building in countries. The strategy outlines the initiatives which WHO Headquarters intends to undertake in the area of strengthening the safety of medicines during the next five years. It will be complementary to the 4-year plan of the Collaborating Centre for International Drug Monitoring and the strategic plans of the member countries participating in the Programme. It was agreed that a small group should be convened to take this forward.

Promoting Safety of Medicines in Children

The manuscript on monitoring the safety of medicines in children was discussed. EMEA have recently published guidelines on the conduct of pharmacovigilance in paediatric populations. These guidelines should be considered in reviewing the text but the WHO manuscript is broader in its concept. However, the regulatory aspects of the text need to be improved and there is a need for a section on medication errors. It was agreed that several members of the Committee should provide input to the manuscript by the middle of April.

Social Marketing of Medicine Safety

The manuscript on the Social Marketing of Medicine Safety was discussed. This script is intended to:

- outline the strategic directions for medicine safety within the WHO Programme in the next decades;
- to develop a strategy for the promotion of medicine safety around the world through a network of dedicated advocates, such as the WHO partners and national centres and
- to provide suggestions on broad tactics, creative ideas and materials which can be used as the basis for promoting drug safety to a wide range of audiences.

It was agreed that the text should be discussed and promoted during the annual meetings of national centres.

Global Networking

A demonstration was made on the use of MedNet, the WHO site for linking partners and projects in WHO programmes. MedNet is hosting over 20 scientific communities. Documents can be shared and revised more easily than by using e-mail. Shared networks are available with security and collaborative e-workspaces. Different countries or subjects can be associated. Membership of communities is controlled by the community. A pharmacovigilance community could be created to exchange, share and communicate information. It was agreed that Vigimed could be elaborated using this system. A community for the Advisory Committee on Safety of Medicinal Products should be set up.

Vaccine collaboration

Recommendations from a global consultation were presented. The aim is to get all adverse events following immunization (AEFIs) to the Uppsala Monitoring Centre (UMC), including from units outside the national pharmacovigilance centres. A person to act as a vaccine focal point is to be recruited to UMC. AEFI programmes should have access to Vigiflow, the online adverse drug reaction reporting system managed by the UMC. Improved advocacy and communication is necessary. The Anatomical Therapeutic Chemical classification system for vaccines needs to be revised. A pilot project in several countries for post-marketing surveillance to improve reporting and signalling is to be developed. There is a working group on safety monitoring needs in an emergency e.g. pandemic 'flu. A rapid alert system is needed for vaccines in a pandemic. Potential coordination with Quality Assurance and Safety: Medicines (QSM) for antivirals during a pandemic is to be discussed. It is planned that a new reporting chain will be set up for use in a pandemic aimed at getting timely information.

Causality assessment

The discussion was introduced by outlining the history of development of the definitions. They were never meant to function as an algorithm. The system is used by over 70% of National Centres and needs to be refined for general use as such. There has been no validation of the system. The US FDA does not use a single system, but does use the principles at times. Different situations need different approaches. For example, drug-induced liver injury has special criteria prepared by an interest group. The hepatologists'

criteria were not designed for regulatory work, but to assist clinical understanding. There are situations where the WHO criteria do not fit well. The primary purpose is to get a clear understanding of the report. When looking at groups of reports, other means need to be considered to establish causality. Some points in the definitions are not exclusive requirements. Reporters often want to know if an event is drug-related. It was pointed out that the initial part of the assessment of a report is a relationship assessment and that this needs to be done using criteria that are as objective as possible. Causality is better established later on clusters of events and looking at other factors such as pharmacology and epidemiology. The general opinion was that the 'WHO method' was valuable and should be retained and improved. It was suggested that International Society of Pharmacovigilance would be a good forum for further discussion. Council for International Organizations of Medical Sciences (CIOMS) may also wish to discuss the issue.

Methodology for evidence of the need for pharmacovigilance

A protocol for collection of data on incidence in selected hospital departments has been developed. This could be used as a baseline for comparisons over several years. It could be undertaken by interns. A pilot project in a few hospitals will be undertaken and the results published at the Annual Meeting of National Centres later this year.

Patient Safety pilot project

This is a collaborative project between the World Alliance for Patient Safety and Medicine Safety and should build upon the success of the WHO Programme for International Drug Monitoring. The problem, the approach and techniques were outlined. An advocacy role is important. One objective is to determine whether National Centres can collect, identify and analyse reports with medication error. It is hoped that the UMC can analyse the pooled data. The future role of National Centres will be assessed. A tool kit needs to be developed. Early experience of the project in Morocco was described. The importance of assessing the preventability of adverse reactions was stressed. Cases already present in the WHO database will be analysed by the end of the year. It was suggested that 'near misses' may not be identified and that these could provide valuable information. Those involved in rational use should be linked to this programme.

Specific Medicines

The Expert Committee on the Use and Selection of Essential Medicines have requested input from ACSoMP on questions on safety in relation to applications for listing in the Essential Medicines List (EML). These need to be of a standard that can be posted on the website and should not contain information that cannot be verified. It is desirable that the assessments should include:

- Critical review of submissions with respect to safety information
- Assessment of comparative safety
- Less emphasis on Summaries of Product Characteristics (SPCs).
- Data from the WHO database.

In the future there will be an emphasis on safety of medicines in children. There is also a need to set up a mechanism for urgent additions and deletions to the EML on the grounds of safety.

Safety assessments and recommendations for the current applications for the EML were as follows:

Cefalexin

It was agreed that cefalexin was acceptable in terms of safety.

Recommendation: Safe for inclusion in EML.

Cefazolin

There are concerns over the number of reports of anaphylaxis associated with cefazolin.

Recommendation: Include in EML with the proviso that it should be used only where rapid resuscitation can be undertaken in cases of anaphylaxis.

Emtricitabine

The recognized adverse reactions include lactic acidosis (usually associated with hepatic steatosis), fat redistribution, exacerbation of hepatitis B (HBV) in patients co-infected with HBV and HIV after emtricitabine withdrawal, immune reconstitution syndrome and osteonecrosis.

Recommendation: It is suggested that, should emtricitabine be included in the EML, the following points should be addressed:

- Safety/efficacy concerns in patients with hepatitis B infection should be highlighted.
- The risks of lactic acidosis/mitochondrial toxicity should be mentioned as a class effect.
- The issue of osteonecrosis should be highlighted with specific advice to patients to seek medical advice if they experience joint stiffness, pain etc.

Emtricitabine + tenofovir

The main safety concern for tenofovir DF is renal toxicity, including renal failure, proximal tubulopathy (including Fanconi Syndrome), nephritis (including acute interstitial nephritis) and nephrogenic diabetes insipidus.

Recommendation: It is suggested that should emtricitabine/tenofovir DF be included in the EML, the following points should be highlighted and addressed:

- Recommendations for monitoring of renal function should be explicit and specified (including information in cases of patients at risk of, or with pre-existing renal disease, i.e. elderly patients)
- Safety/efficacy concerns in patients with liver dysfunction, chronic hepatitis and in the context of concomitant use with other antiretrovirals should be highlighted.

Fluoxetine

The adverse effect profile is well known and adequately described. Fluoxetine is better tolerated than tricyclic antidepressants (TCAs) considered as a group and is better tolerated in comparison with individual antidepressants, in particular amitriptyline. The relationship between SSRIs and suicide has been the focus of several investigations.

Recommendation: Safe for inclusion in the WHO EML.

Paromomycin

More data including from different settings like AIDS, paediatric populations and elderly people users is very important. It is desirable to have Phase IV studies to identify new safety and effectiveness issues [e.g., drug-drug and drug-food interactions] in real world situations related with the new indication and new settings.

Recommendation: It is premature to include paromomycin in the EML. There is insufficient evidence of its safety in the treatment of visceral leishmaniasis.

Ribavirin

This medicine has not been evaluated in children and the elderly. The drug has been shown to be teratogenic in animal at doses lower than therapeutic dose. The drug accumulates.

Recommendation: The application is for ribavirin for treatment. There should be some comments / statement on the use of ribavirin in post-exposure prophylaxis. The drug is likely to be used / misused for prophylaxis where the benefit / risk could be quite different from when used for treatment.

Simvastatin

Increased risk of rhabdomyolysis with acute renal failure is associated with the use of simvastatin. As reversible increase in levels of serum aminotransferases may occur, liver function of the patient must be assessed before the start of the treatment with simvastatin.

Recommendation: Simvastatin may be added to the complementary list of the EML. There needs to be careful monitoring.

Sumatriptan

Adverse reactions are common but the great majority are minor and evanescent.

Although reactions are common, use of sumatriptan with the appropriate precautions is safe. There has been widespread use with few convincing serious reactions.

Recommendation: From the safety point of view, sumatriptan 50 mg tablets can be recommended for inclusion in the EML.

Tenofovir

Recognized adverse reactions include lactic acidosis (usually associated with hepatic steatosis), fat redistribution, exacerbation of hepatitis B (HBV) in patients co-infected with HBV and HIV after tenofovir withdrawal, immune reconstitution syndrome and osteonecrosis.

Recommendation: Tenofovir should initially be placed on the "Complementary List" in view of concerns regarding the feasibility of renal monitoring in developing environments.

Amodiaquine/artesunate

There have been reports on adverse events associated with the use of artesunate amodiaquine in several African countries, most reliably reported in Ghana. The review of these reactions suggested that once daily exposure to artesunate 200 mg/amodiaquine 600 mg was common to all events, making it plausible that these effects are dose dependent.

Recommendation: It is premature to include amodiaquine-artesunate in the EML. An appropriate risk-management plan must be drawn up to address the dosage issues before contemplating inclusion of amodiaquine-artesunate in the EML.

Levamisole

In 1994-2003, 632 cases of imidazoles-induced demyelinating encephalopathy were reported in the domestic literature in China, of which 543 cases were levamisole-induced. The causality of levamisole and demyelinating encephalopathy has been investigated and demonstrated by six pharmacoepidemiological studies. The WHO global database contains 81 case reports of central nervous system disorder.

Recommendation: Levamisole should be deleted from the EML because of the availability of safer products. However if resistance becomes a problem with the alternatives, it could be used as a second-line treatment.

Other specific medicines

Thalidomide

Foetal abnormalities with thalidomide are still being reported. The situation in Brazil is complicated by about 30 indications for use and the difficulty in controlling its use. Clear messages about risk management and minimization are needed. The Committee agreed that pressure should be put on governments to address this issue. If thalidomide is licensed, adequate control measures must be in place.

Generic reporting form

A discussion took place on the pros and cons of developing a generic reporting form. The content and design need to be considered. Forms often need to be adapted to local situations. Another complication is the expanding nature of pharmacovigilance that requires new types of data e.g. medication error. Over the years all countries participating in the WHO Programme for International Drug Monitoring have developed their own forms to suit their own needs in spite of the existence of other models. Guidelines for designing a form should be developed.

Any other matters

The methodology developed by the New Zealand Intensive Medicines Monitoring Programme (IMMP) is of great value in promoting medicine safety. Discontinuing the IMMP would be a real loss to worldwide pharmacovigilance.

Letters to the WHO Pharmaceuticals Newsletter

In WHO Pharmaceuticals Newsletter No. 2, 2006 we published an article by Professor Marcus Reidenberg with the title 'We should not say 'drug safety' when we mean 'drug toxicity''. Professor Reidenberg wrote that the term 'drug safety' could mislead the average person into assuming that a medicine is safe; when, in fact, drug toxicity or an adverse drug reaction is what is being discussed. Taking his cue from George Orwell's '1984', Professor Reidenberg argued that we must avoid 'newspeak' and must not promote a term which 'appears to be a euphemism for an adverse drug reaction programme'.

Below, we bring you Mr Ray Skinner's comments to the article, followed by Professor Reidenberg's response.

Dear WHO Pharmaceuticals Newsletter,

I refer to the editorial and the article in the WHO Pharmaceuticals Newsletter No, 2, 2006, a copy of which I recently received at my office.

While I would hesitate to contradict Prof Reidenberg outright – he has raised a very valid question – I wonder if perhaps we are in danger of running counter to a necessary and humane cultural tradition of hopefulness that is almost universal in societies. Speaking of risk in terms of 'safety' may not be scientifically as accurate or coldly logical as one might favour, but I don't think it is fundamentally dishonest or misleading. It certainly seems to me to express a more positive and hopeful viewpoint. To say "this is safe within limits, as far as we can test and tell", will certainly encourage the recipients of medicines (i.e. the patients) to appropriate confidence in their treatment, while to tell them "This is frankly dangerous – watch out for this, and this", would undoubtedly produce demonstrable negative effects in care. I'd be surprised if this had not already been verified by research. In the average mind, and with human cultures, languages, and thought conventions being what they are, I should think it very predictable to see a significant drop in public confidence in medicines if we suddenly change our tack from "We are here, in an honest scientific attempt to protect and promote your health and safety" to a more negative "We are here to monitor your drug disasters, and maybe we can help after the event, (or not, as the case may unhappily turn out)". I agree the latter may be ruggedly honest, and ruthlessly scientific, but I am not sure that it is altogether kind or even very useful.

Scientifically we may not like it, but there it is. Like the good Professor, I too care very little for political doublespeak, but we do have to wrestle with the human element. It is probably true that no vocabulary anywhere is ideologically neutral, anyway. If the common understanding and convention of using positive terms to deal with what appear to be scientifically negative issues is in fact useful for human communication, why do we have to fight it?

Is the universal ideology of hopefulness - that medical things for sale or to be given on prescription are 'safe' and of 'good quality' - as unreal or as inappropriate as Professor Reidenberg might seem to hold? On his logic, and applying the argument to other relevant areas of life and thought, we would have to refuse to talk of quality management, and instead have only risk management – which is the same thing for all practical purposes. We might as well talk of Ministries of Illness instead of Department of Health. But it wouldn't help public confidence, and the negative placebo effect on services and health outcomes would be quite awful. Would we have to then talk about medical wounding, instead of 'surgery'? Because that's what it is, with all its known risks, but we don't speak like that to them, either, do we?

For me the key question is a practical one having regard to success in pharmacotherapy, not a merely scientific accuracy in drug regulatory activities. What people really want to know about medicines is normally expressed in positive terminology. I see no real reason to challenge that. Positive language always expresses an unspoken and corresponding negative aspect, does it not? We say good, and we know evil is there. We say right, and we know wrong is there. We say road safety, and we all know quite well that it is risks and hazards that we are talking about, and what we are seeking to minimize. But mostly, I think, people want and need the more positive lead in the presentation. It helps them focus better and move ahead more positively – in hope, rather than having to convince themselves every day to slog it out against the negative correspondent: despair.

Yours kindly,

RAY SKINNER
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Professor Marcus Reidenberg's reply to Mr Ray Skinner:

Mr Skinner makes an important point of not abandoning patients by taking away their hope. I agree with this but think taking away hope is a very different issue from using euphemisms or even words that have different meanings to minimize or hide the idea that medications have adverse effects. As a society, we have acted with great surprise when confronted with a trial of rofecoxib vs placebo showing the NSAID caused some heart attacks (1). The possibility that COX-2 inhibitors could cause heart attacks was predicted based on the drug's pharmacology (2) and was demonstrated in an early clinical trial (3,4). We are astonished at the possibility of antidepressant medications causing suicidal ideation in adolescents (5) even though we know that the risk of suicide increases during the early phase of effective drug therapy for depression. As a society, we have been led to believe that medicines are safe when, in truth, they are not free from the possibility of doing harm.

In addition, we often express the extent of benefit in a way that exaggerates its magnitude. For example, the antidepressant drugs are described as effective, yet in a representative randomized double-blind placebo-controlled study, 48% of all placebo recipients responded. The response rate of the two drug treatment groups was only 4% and 16% better than that of the placebo-treated patients. Because the patient groups were large enough, the difference between placebo and one of the study drugs was statistically significant. The authors concluded that this drug was "efficacious for the treatment of major depression" (6). Yet, because the better of the two study drugs was only a little bit better than the placebo, it was ineffective in the majority of the patients who needed it. Clearly stating that it is effective without qualification is misleading according to the dictionary definition of "effective". My point is that there is nothing unusual about this study. It is really representative of how study results are interpreted. This interpretation leads to exaggerated expectations and disappointment when reality sets in. The "significant drop in public confidence in medicine" that Mr Skinner mentioned has already occurred in the United States. The reason is that some medicines previously promoted as safe are not. It is not because of Mr Skinner's concern that if people would learn the complete truth at the outset, they would lose confidence. It was that people were not told the complete truth at the outset and do not know if they are being told the full truth now. Credibility lost is hard to regain.

What people really need to know about medicines is what they actually do. The words "safe" and "effective" have specific defined meanings. When we knowingly use these words to mean something different when describing a drug's effects, we are deceiving the listener or reader. I think deception has no place in medicine.

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References:

1. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma prevention trial. *The New England Journal of Medicine* 2005; 352: 1092-1102.
2. Fitzgerald GA, Patrono C. The Coxibs, Selective Inhibitors of Cyclooxygenase-2. *The New England Journal of Medicine* 2001; 345: 433-42.
3. Bombardier C, Laine L, Reicin A., et. al. Comparison of upper gastrointestinal toxicity of Rofecoxib and Naproxen in patients with Rheumatoid Arthritis. *The New England Journal of Medicine* 2000; 343: 1520-8.
4. Mukherjee D, Nissen SE, Topol EJ. Risk of Cardiovascular Events Associated with selective COX-2 Inhibitors. *The Journal of the American Medical Association* 2001; 286: 954-959.
5. Ryan ND. Treatment of depression in children and adolescents. *Lancet* 2005; 366: 933-940.
6. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *The Journal of Clinical Psychiatry* 2002; 63: 225-31.