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Editor's Notes

In this issue we are starting a round of the Regional Pharmacovigilance Units. These are part of the National Pharmacovigilance System and are in a privileged position to interact with their region's health professionals who are a potential source of ADR reports. First off we present the Southern Pharmacovigilance Unit, which receives directly the reports coming from professionals in the Algarve and Alentejo regions.

A new segment – "In the literature" – consists of a journal club for pharmacovigilance and related articles, with a special emphasis on practical topics. "In the literature" opens with a summary of an interesting review from Drug Safety which is indeed a matter of taste!

Oral norfloxacin: no longer indicated for complicated pyelonephritis

Norfloxacin is a fluoroquinolone antibacterial agent. Oral formulations of medicines containing norfloxacin are authorised in several member states of the EU under varying trademark names. They have been indicated for the treatment of infections, including complicated and non-complicated urinary tract infections, prostatic infections, non-complicated gonorrhoea, various types of gastroenteritis and conjunctivitis.

These recommendations do not apply to the use of norfloxacin in other types of infections, such as non-complicated urinary infections.

It is therefore recommended to doctors that they:

- **not prescribe oral norfloxacin in complicated pyelonephritis**

- consider **substitution** with another antibiotic in patients with complicated pyelonephritis who already are being treated with norfloxacin.

Additional information can be found at the EMEA site at:
http://www.emea.europa.eu/pdfs/human/press/pr/38026008en.pdf

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
PIL	Patient Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

How can I report an adverse reaction?

Postage Paid Card
yellow *(physicians)*, **purple** *(pharmacists)* **or white** *(nurses)*

Also online at:
www.infarmed.pt/pt/vigilancia/medicamentos/reacções_adversas/fichas_notificação/index.html

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Oral Moxifloxacin: Indications restricted

Moxifloxacin is a fluoroquinolone antibiotic. Oral formulations of medicines containing moxifloxacin are authorised in several EU member states, under differing trademark names, for the treatment of acute exacerbations of chronic bronchitis, acute bacterial sinusitis, and community-acquired pneumonia. In some countries they are also indicated for mild to moderate inflammatory pelvic conditions.

Following on questions regarding hepatic safety of orally administered moxifloxacin, EMEA has reviewed all its available safety information, and has concluded that the benefits of oral moxifloxacin still outweigh its risks. Nevertheless, on account of safety issues mostly pertaining to an increased risk of hepatic adverse reactions, the following recommendations have been made:

- In acute bacterial sinusitis and in acute exacerbations of chronic bronchitis, oral moxifloxacin should only be used whenever, after an appropriate diagnosis, **other antibiotics cannot be used**, or **therapy with the latter is not effective**.

- In community-acquired pneumonia, this antibiotic should only be used in those cases where **no therapeutic alternative** is available.

Moreover, warnings have been further underscored in relation to **the risk of diarrhoea, cardiac failure in females and in the elderly, serious skin reactions, and fatal liver damage**.

The use of parenteral moxifloxacin is not affected by the above reassessment.

Doctors should prescribe oral moxifloxacin in accordance with the SPC (which is going to be updated) and with the national guidelines on the use of antibiotics.

For further information go to the EMEA site at:
http://www.emea.europa.eu/pdfs/human/press/pr/38292708en.pdf

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Southern Pharmacovigilance Unit:
Meeting the challenges of safety profile assessment head-on

The Southern Pharmacovigilance Unit is part of the National Pharmacovigilance System and is based at the Lisbon University School of Pharmacy. Its catchment area includes the southerly regions of the **Algarve and Alentejo**.

Ever since it started operating, this Unit has envisioned pharmacovigilance as subject that is constantly evolving, dynamically keeping up with new regulatory requirements, the evolution of pharmaceutical technologies, as well as with the safety expectations patients and other stakeholders have regarding medicines. This vision is mirrored by a **growing number of ADR reports**: comparatively to the same period of time in the preceding year ADR reports went up 8% in 2007, and this year they have so far increased **20%**.

The main goal of pharmacovigilance activities is to achieve the highest possible level of safety for patients taking pharmacological therapy. In order for this objective to be reached, robust evidence must be generated which is up to date with the emerging challenges in medicines safety profile assessment, and at the same time is able to respond to other already existing challenges. Developments in the pharmaceutical industry, innovative biotechnological medicines, new chronic therapies, and treatments for risk factors in anticipation to the clinical manifestations of certain diseases – these are all welcome benefits for patients which call for an adequate epidemiological response in terms of safety profile surveillance.

There is a fundamental epidemiological model for generating evidence: **spontaneous ADR reporting**. No other model shows such an **advantageous cost-effectiveness** relation in detecting rare and unexpected adverse reactions. In fact, reporting a **rare and/or unexpected adverse reaction** may have an impact on public health that is all the more significant than the reporting agent needs merely fill out an ADR report form. Still, there other models to be taken into account, which act synergistically with spontaneous reporting for the benefit of patients.

In order to face up to these challenges, the Southern Pharmacovigilance Unit has been focusing mainly in three major areas: Training, Cooperation and Research.

Training health professionals is important to disseminate knowledge on spontaneous reporting, in that this is the core epidemiological model in pharmacovigilance. This Unit has rolled out dozens of training sessions and seminars in health centres and hospitals, participated in pre-graduate training, as well as in post-graduate training (the Unit has taken part in eight Master's programmes).

Cooperation with health professionals has been reinforced with the help of hospitals from our catchment area, through creating and providing a framework to pharmacovigilance promoters which can be construed as a preview of future pharmacovigilance delegates. This partnership, though recent, has strengthened communication channels and mutual ability to obtain safety data. The success of this project leads us to believe that health professionals from other health units will probably be receptive to it, and a so-called pharmacovigilance delegate might in the future be of mutual benefit.

We have outlined a **research** plan which aims both to roll out innovative projects (such as active post-vaccination event surveillance) and to develop and apply analytical tools to generate safety signals through database statistic analyses. With these research projects we aim to obtain data that will allow us to pinpoint safety problems with greater scientific efficiency (fewer instances needed until the problem is finally detected) and greater granularity (ability to tell apart smaller risk differences).

In short, this pharmacovigilance unit's activity strengthens those pharmacovigilance practices that are essential for the safety profile of medicines to be assessed, and simultaneously tests and analyses new epidemiological models that may further benefit spontaneous reporting.

Quite naturally, all these activities would be nothing but impossible had we not the contribution of all those health professionals who report ADRs or otherwise collaborate with us. We are very thankful and aware of the importance of their cooperation, and are eager to respond to any doubt or suggestions they may wish to put forward to us.

UFS

Viracept:
Studies evaluated by EMEA suggest there is no increase in the risk of cancer in patients who took this medicine when contaminated with ethyl mesylate

Viracept is an antiretroviral which is used in combination with other antiretrovirals for the treatment of adults, teens and children older than 3 years infected with HIV 1.

In June 2007, following a recommendation from EMEA, the European Commission suspended Viracept's MA due to contamination of some batches of this medicine with high levels of ethyl mesylate, a known genotoxic (which therefore can harm human DNA). Later on the medicine's MA Holder demonstrated that the manufacturing problem that had caused contamination had already been eliminated. In October 2007, the CHMP at EMEA recommended that the MA suspension be cancelled.

Nevertheless, the CHMP did request that various toxicological studies be carried out, so that the potential risk for patients exposed to ethyl mesylate contaminated Viracept could be ascertained. Studies performed by the MA Holder demonstrated that it is possible to calculate a threshold below which ethyl mesylate cannot cause any irreversible damage (mutation) in DNA. The CHMP stressed that the patients or children whose mothers took contaminated Viracept during their pregnancy **had been exposed to levels of ethyl mesylate well below threshold**. There is therefore no increased risk of cancer in these patients when compared to patients who were never exposed to the contaminant.

The Committee therefore concluded that, unlike what had initially been planned, **there is no need to monitor patients who were exposed to high levels of contaminated Viracept** through specific patient records

For further information please go to the EMEA website at:
http://www.emea.europa.eu/humandocs/PDFs/EPAR/Viracept/38225608en.pdf

Epoetins:
New warning on their use in cancer patients

The EMEA CHMP has reviewed new data emerging from studies which have demonstrated an increased risk of tumour progression, venous thromboembolism, and reduced global survival in cancer patients who have received epoetins, comparatively to patients who have not.

Following this review, the CHMP concluded that the **benefits** of epoetins still are **higher than their risk**, **except** in cancer patients with a reasonably long life expectation. In these cases, anaemia should preferentially be corrected by means of blood transfusions.

Physicians and patients are reminded that the decision to administer epoetins should be based on carefully informed consideration of individual risks and benefits, taking into account the type and stage of the tumour, the magnitude of the anaemia, the patient's life expectancy, the environment in which the patient is being treated, as well as his/her own preferences.

These new data have no impact on the use of epoetins for the treatment of anaemia in chronic renal failure patients.

See: Circular Informativa n.º 113/CD from 26-06-2008 online at:
http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/DETALHE_ALERTA?itemid=1015787

Magda Pedro

In the literature…
A matter of taste: medicine-related dysgeusia

Doty RL, Shah M, Bromley SM. Drug-induced taste disorders. Drug Safety 2008;31(3):199-215

Review from Drug Safety. The authors are affiliated with the University of Pennsylvania Smell and Taste Center (USA).

Medicines, quite like food supplements and medicinal herbs, can cause chemo-sensorial disturbances, namely disorders of taste and smell. The latter may sometimes be prolonged, and thus significantly alter the patients' appetite, food ingestion, quality of life quality and emotional stability, as well as their compliance with therapeutic regimes.

Unfortunately, although this type of collateral effects is mentioned as frequent in the medicine's profiles (see Table), in reality the available empirical studies are few and little is known about their pathophysiological basis.

Both doctors and other health professionals further compound this problem by sometimes erroneously ascribing to a gustatory dysfunction the loss of **taste for chocolate, lemon, meat sauces, and strawberry**, when in fact loss of detection of these flavours is related to **decreased stimulation of olfactory receptors** by the retronasal channel.

True losses of the sense of taste reflect taste bud mediated sensations, namely **sweet, sour, bitter, salty, unami** (e.g.: the gustatory sensation given by sodium glutamate, which is typically used in Oriental cuisine), and possibly also **chalky** (e.g.: calcium salts), **metallic** (e.g.: iron salts) and **fatty**.

Finally, the descriptions found often do not make a distinction between (quantifiable) sensorial loss and either distortions/perversions of taste or phantom tastes.

Medicines that may alter smell and/or taste (according to the US Physician's Desk Reference)

Pharmacological Class	Agent
Anxiolytics	Alprazolam, buspirone, flurazepam
Antibacterials	Ampicillin, azithromycin, ciprofloxacin, clarithromycin, enoxacin, temabutol, metronidazole, ofloxacin, sulfamethoxazole, ticarcillin, tetracycline
Antidepressants	Amitriptyline, clomipramine, desipramine, doxepine, imipramine, norttriptyline
Antiepileptics	Carbamazepine, phenytoin, topiramate
Antifungals	Griseofulvin, terbinafine
Antihypertensives and cardiovascular medicines	Acetazolamide, amiodarone, amiloride, bepridil, betaxolol, captopril, diltiazem, enalapril, spironolactone, hydroclorothiazide, losartan, nifedipine, nisoldipine, nitroglycerine, propafenone, propranolol, tocainide
Antihistamines (descongestant)	Chlorphenamine, loratadine, pseudoephedrine
Antiinflamatory agents	Auranofin, beclomethasone, budesonide, colchicine, dexamethasone, flunisolide, fluticasone (propionate), penicillamine, gold salts
Antimanic agents	Lithium
Antimigrainous agents	Dihydroergotamine (mesylate), naratriptan, rizatriptan, sumatriptan
Antineoplastic agents	Cisplatinum, carboplatin, cyclofosfamide, doxorubicin, fluorouracil, levamisole, methotrexate, tegafur, vincristine
Antiparkinsonians	Anticholinergic agents, levodopa
Antipsychotics	Clozapine, trifluoperazine
Antivirals	Acyclovir, amantadine, gancyclovir, interferon, pirodavir, oseltamivir, zalcitabine
Bronchodilators	Bitolterol, pirbuterol
CNS stimulants	Amphetamine, dexamphetamine, methylphenidate
Hypnotics	Eszopiclone, zolpidem
Hypolipaemic agents	Atorvastatin, fluvastatin, lovastatin, pravastatin
Muscle relaxants	Baclofeno, dantrolene
Pancreatic enzymes	Pancreatic lipase
Smoking cessation aids	Nicotine
Medicines acting on the thyroid	Carbimazole, sodium levothyroxine and related agents, propylthiouracil, thiamazole

Among those medicines which may alter smell and/or taste, the article's authors highlight the commoner pharmacological groups that are described below.

Antibacterials

- **Many** antibiotics have a **bitter, metallic and/or sour** taste, when in concentrations high enough to be excreted in saliva.
- It is well known that **metronidazole** (e.g.: in Helicobacter eradication regimes) can cause a metallic taste that may affect therapy compliance.
- How antibiotics taste can be influenced by the milieu in which they are ingested. Thus some, **when taken with acid foods or suspended in sports drinks**, are bitterer than when taken with water only. Indeed, those medicines dissolve faster in an acid environment, their bitter taste left unchecked by sweeteners.

Antifungals

- **Griseofulvin** can reportedly cause ageusia (total loss of taste).
- The case of **terbinafine** is extensively documented. According to the literature, taste is recovered in most cases until up to several months after the drug has been discontinued. In this case, the olfactory function seems to be normal. Perception of sour (**citric acid**) and bitter (**caffeine**) is more affected than sweet (sucrose) and salty (sodium chloride). Assuming that, as in primates, humans should possess fewer afferent fibres with a preferential specificity for sour and bitter, this could explain how this range of the taste spectrum could more easily be loss.
- This type of ADR seems to be commoner in **older** patients and in those with **smaller body mass**. In fact, terbinafine is highly lipophillic and the loss of taste may reflect, for the same dose, higher blood concentrations. Furthermore, in the elderly, taste afferents are at the outset fewer or less functional.

Antivirals

- Taste alteration ADRs can sometimes be of great magnitude, usually on the side of **bitter**. **HAART** regimes may be associated with a high incidence of taste perversion in adult HIV-positive patients, including an **oily** aftertaste.
- Similarly to antibacterial agents, the sensation of bitterness increases when antivirals are taken in an **acid milieu**.

Antineoplastic chemotherapeutic agents

- These can cause both olfactory and gustatory receptors to be destroyed.
- Initial infusion of a number of antiproliferative agents such as cisplatinum can cause an **immediate bitter taste**, as well as changes that can last from weeks to months, which may or may not reflect the passage of the drug into saliva.
- **Secondary immunosupression** can lead to oral candidosis, as well as haemorrhage and periodontal disease which, on their turn, potentiate dysgeusia.
- Ageusia has recently been reported in a patient with multiple myeloma undergoing therapy with **liposomic pegilated doxorubicin**.

Antithyroid agents

- **Taste and smell** changes are described in the literature.
- On the other hand, patients with hypothyroidism more often report gustatory alterations than non-hypothyroid patients. This finding could be explained by the fact that hormonal replacement therapy with thyroxin brings back to normal levels their characteristically raised thresholds for detection of bitter.

Cardiovascular medicines

- Alterations of the sense of taste are described for **almost every drug class** under this heading.
- **ACE inhibitors** are the antihypertensive drugs that are more frequently associated with adverse taste effects, especially captopril and, more rarely, enalapril. They can make **sweet foods taste salty**, or produce a **bitter or salty** aftertaste. These effects are dose related, and withdrawing the medicine can clear the problem in a few days or up to a few weeks. The response of one same patient is **variable** for different ACE inhibitors.
- **Calcium channel antagonists** and **angiotensin II antagonists** such as losartan have been associated with dysgeusia, though less frequently than with ACE inhibitors.
- **Amiloride** is bitter and is sometimes associated with dysgeusia. ▶

▶ Carbonic anhydrase inhibitors such as acetazolamide (used for glaucoma and for prevention of altitude sickness) often cause taste disturbances.

● Dysgeusia, ageusia and parosmia are reportedly associated with several **statins**.

Corticosteroids

● These can cause oral candidosis, stomatitis, glossitis, haemorrhage and dental disease.

● In one study [Mitchell & Counselman], it was seen that among orally administered formulations, **dexamethasone** is more pleasant to the taste than prednisone or prednisolone.

● Also, in the case of intranasally administered drugs, **triamcinolone** has been shown to cause fewer taste disturbances than momethasone or fluticasone propionate.

Antidepressants

● Several **tricyclic antidepressants** have a specific taste and/or change the intensity of other tastes such as salty or sweet. A characteristic adverse effect of this pharmacological class-dry mouth-can be a major contributory factor for dysgeusia.

● **Selective serotonin reuptake inhibitors** have also been associated with taste loss or perversion. Besides, fluoxetine is associated with parosmia.

● Dysgeusia may result from an **interaction** with other medicines which can also potentially cause taste disturbances, namely antibiotics.

Anxiolytics and Hypnotics

● Although **benzodiazepine** associated dysgeusia is reported, there is evidence that this pharmacological group can **potentiate taste** and increase the perception of the sweet flavour of some foods.

● ADRs consisting of **taste perversion and parosmia** have been ascribed to hypnotics such as zolpidem.

Antipsychotics and Humour stabilisers

● Haloperidol, as well as others like olanzapine and risperidone, for instance, have been associated with **dysgeusia**. This specifically concerns the bitter taste in the case of risperidone.

● It is not known whether the taste perversion that may occur with **lithium salts** results from a direct effect on the gustatory sense, on the olfactory sense, or on both.

Antiepileptics

● A taste perception distortion commonly occurs with **topiramate**, though this problem can fade as treatment carries on or with dose reduction.

● Sweet dysgeusia can be associated with **hyponatraemia** resulting from the antidiuretic hormone inappropriate secretion syndrome caused by carbamazepine or oxcarbamazepine, for example.

● Although **gum hyperplasia** is a classic phenytoin ADR (also of cyclosporin and calcium channel blockers), there is no clear correlation with dysgeusia.

Central Nervous System stimulants

● These may be associated with **dysgeusia** and **aberrant oral sensations**.

Medicines for the treatment of drug addiction

● **Bupropion** (used for tobacco addiction) commonly causes taste disturbances associated with mouth dryness.

● **Disulfiram** can leave a metallic or garlicky aftertaste.

● **Naltrexone** may dampen the pleasantness of the sweet taste, or decrease the normal tendency for food to be perceived as all the more pleasant the greater the sensation of hunger.

Approach to taste ADRs

Long-term persistent gustatory ADRs can be due to a lesion of peripheral taste receptors, of neuronal pathways or even of central structures. Unfortunately a time frame for expectation of reversibility of many of these effects is not known.

Generally speaking, taste related adverse reactions may be related to:

a. The medicine's own taste.

b. Direct or indirect harm (e.g.: via gastroesophageal reflux) of taste receptors.

c. Sequellae from immune suppression (e.g.: oral candidosis).

d. Disturbance of nervous transmission through interference with neurons or neurotransmitters.

e. Changes in higher cortical processing of taste related sensorial data.

f. Dryness of the oral mucosa resulting in limited access of chemical substances to their receptors.

g. Changes in the production or composition of saliva and mucous secretions – saliva is essential as an acid and base buffer, as well as for increasing the availability of solubilised chemicals for their corresponding gustatory receptors.

The patient's **expectations** can also compound this problem. Should a patient expect some medicine to display an unpleasant taste, then it is probable that it will be perceived as such. The patient's own socio-cultural background and previous experience may also influence their perception of taste.

In most cases, the more logical approach consists of **discontinuing** the drug and replacing it with an alternative medicine, or **lowering its dose**. When making such decisions the **risk-benefit ratio** should be considered first and foremost, and one should bear in mind that repetitive or continuing exposure to a given medicine may lead to tolerability or even preference for it.

The potential role of other **conditions or concomitant medicines** should also be considered. **Good oral hygiene** is important, as well as excluding **excessive use of oral gargle solutions** and **repetitive trauma** associated with dental misalignment, prostheses or excessively forceful dental cleaning, for instance. For dry mouth, artificial saliva may be useful.

The authors stress that epidemiological and experimental data are scarce. Reporting this type of adverse reactions, once excluded confounding factors such as the above, is therefore of great importance to increase our knowledge on the profile of many commonly used medicines, as well as to ensure the patients' safety and well-being.

How frequent, how rare an ADR?*

Very common:	**≥1 case per every 10 exposed**
Common:	**≥1/100 but <1/10**
Uncommon:	**≥1/1,000 but <1/100**
Rare:	**≥1/10,000 but <1/1,000**
Very rare:	**<1/10.000**

*MedDRA frequency convention

Medicinal Plants from A to Z
described adverse reactions

• **European Elderberry** *(Sambucus nigra)*
- nausea, vomiting, toxicity (stems and leafs)

N.º of Medline citations: 4
Main uses described: anti-influenza, spasmolytic, laxative.

• **Sage** *(Salvia officinalis)*
- nausea, vomiting
- seizures (oil)

N.º of Medline citations: 16
Main uses described: spasmolytic, antioxidant, oral and vaginal hygiene.

NB 1: The main uses are those most frequently described in the literature irrespective of evidence of effectiveness. Their presentation herein is factual and does not mean that therapeutical uses mentioned are approved or implicitly condoned in any way by this publication.
NB 2: The number of Medline citations is merely intended to give an idea of the magnitude of publications on adverse reactions associated with the product. Key-words used: "human side effects", "toxicity in humans", "adverse reactions".