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THESYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

18 ANNIVERSARY

Release sustained strength against COPD with 24-hour Onbrez® Breezhaler®

Onbrez® Breezhaler®

The only Ultra[1] - LABA offers patients[2]:

- ✔ Superior lung function improvement (FEV_1 vs salmeterol and formoterol)
- ✔ Rapid onset of action within five minutes from the first dose
- ✔ Significant reduction in the use of and need for rescue medication
- ✔ A good overall safety and tolerability profile
- ✔ Available in 150µg and 300µg: two dose strengths allowing flexibility when treating patients with COPD
- ✔ Onbrez® Breezhaler® allows patients to hear, feel and see that they have taken the full dose correctly

Onbrez Breezhaler (indacaterol) inhalation powder, hard capsules
PRESENTATION: Onbrez Breezhaler 150mcg and 300mcg inhalation powder hard capsules containing indacaterol maleate, and separate Onbrez Breezhaler inhaler. INDICATIONS: For maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** Recommended dose is the inhalation of the content of one 150mcg capsule once a day, administered at the same time of the day each day, using the Onbrez Breezhaler inhaler. Dose should only be increased on medical advice. The inhalation of the content of one 300mcg capsule once a day has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. Maximum dose is 300mcg once daily. No dose adjustment required in elderly patients, for patients with mild and moderate hepatic impairment or for patients with renal impairment. No data available for use in patients with severe hepatic impairment. No relevant use in the paediatric population. If a dose is missed, the next dose should be taken at the usual time the next day. Onbrez Breezhaler capsules must not be swallowed. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, to lactose or to any of the other excipients. **WARNINGS/PRECAUTIONS:** *Asthma:* Onbrez breezhaler is a long acting beta2-adrenergic agonist, which is only indicated for COPD and should not be used in asthma. Long-acting beta2-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma ***Paradoxical bronchospasm:*** If paradoxical bronchospasm occurs Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted. ***Deterioration of disease:*** Not indicated for treatment of acute episodes of bronchospasm, i.e. as rescue therapy. ***Systemic effects:*** Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. ***Cardiovascular effects:*** Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes. In case such effects occur, treatment may need to be discontinued. ***Hypokalaemia:*** Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. ***Hyperglycaemia:*** Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients. During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1.2% on Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus. ***Pregnancy and Lactation:*** No data available from the use of indacaterol in pregnant women. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. Not known whether indacaterol / metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or discontinue Onbrez Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Immediate hypersensitivity reactions have been reported after administration of Onbrez Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Onbrez Breezhaler should be discontinued immediately and alternative therapy instituted. **INTERACTIONS:** Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists.Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Indacaterol should not be given together with beta-adrenergic blockers (including eye drops) as these may weaken or antagonise the effect of beta2-adrenergic agonists. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler. Indacaterol has not been shown to cause interactions with co-medications. **ADVERSE REACTIONS:** The most common adverse reactions with Onbrez Breezhaler are: dizziness, nasopharyngitis, upper respiratory tract infection, sinusitis, , headache, , cough, , rhinorrhoea, respiratory tract congestion, muscle spasm, peripheral oedema. Common: Chest Pain, Oropharyngeal pain including throat irritation, Uncommon: Myalgia, Musculoskeletal pain, Pruritis/rash, Paradoxical bronchospasm, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia ,paraesthesia, atrial fibrillation and non-cardiac chest pain, ischaemic heart disease. Please refer to SmPC for a full list of adverse events for Onbrez Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Onbrez Breezhaler 150mcg - carton containing 10 or 30 capsules and one Onbrez Breezhaler inhaler. Onbrez Breezhaler 300mcg - carton containing 30 capsules and one Onbrez Breezhaler inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/593/001, 002, 007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +35621222872. 2014-MT-ONB-25-Sept-2014

References
1. Gazzola M, Matera MG. Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol. 2008;155:291-299.
2. Novartis Europharm Ltd. Onbrez® Breezhaler® Summary of Product Characteristics.

NOVARTIS PHARMACEUTICALS

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breezhaler®
indacaterol inhalation powder

ONB Ad 1 10/14 MT

RACISM & CARDIOLOGY – A PARADOX

The Maltese Cardiac Society Conference 2014 was held on the 17-18th October where it attracted a record participation of around 500 attendees. Indeed, locally we have made significant advances in this field, which are usually more aptly attributed to larger countries. One such technology is the **Transcatheter Aortic Valve Implantation** (TAVI). This minimally invasive surgical procedure replaces the heart valve without actually removing the damaged one. Locally, a transfemoral approach is used to carry out this procedure. In essence, it means that there is no need to open the chest to insert the new valve and the patient can return home after a couple of days.

At this stage I would like to take you back to December of 1967, when the first human heart transplant was carried out. This was carried out by a South African cardiac surgeon, Christiaan Barnard, utilizing the techniques developed and perfected by Norman Shumway and Richard Lower. He performed the transplant at the Cape Town's Groote Schuur Hospital. All the medical team was caucasian, with the exception of Hamilton Naki who was Barnard's black assistant. Although Naki never received a formal medical education, he was recognised for his surgical skills and for being able to teach such skills to medical students and physicians alike. In fact, Barnard specifically wanted him on his team during this first transplant procedure.

Nothing exceptional, you might say. However, in order to appreciate its significance, one must understand that in Africa, at that time, there was apartheid. Black people were not allowed to operate on caucasians or even enter operating theatres during such interventions. These, among the plethora of other restrictions, of course. In fact, the exceptionality of Naki's contribution has also been captured on the silver screen through *Hidden Heart,* a documentary released in 2008.

Notwithstanding the restrictions imposed through apartheid, on 2 January 1968, Barnard performed a second operation by transplanting the heart of a young black man, Clive Haupt, who had died the previous day from stroke into a 58-year-old Caucasian dentist named Philip Blaiberg. Blaiberg survived the operation, and survived for 19 months (the first heart transplant patient died 18 days after the operation).

At this stage, I question whether these historical anecdotes, by their very nature, are reminiscent of the paradoxicality of human nature.

Ian Ellul

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18 years of service

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MMSA

Relvar Ellipta is for patients (≥12 years) in need of asthma maintenance therapy[1]

Asthma

Because I simply don't have space for asthma

For patients like Maria, every day is full on, so even small reminders of asthma can have an impact. So, when they're uncontrolled on ICS alone, choose new Relvar Ellipta:

- The first ICS/LABA combination to deliver continuous 24-hour efficacy[2]
- In a practical, once-daily dose[1]
- Delivered in an easy to use device that patients prefer to their current inhaler[3,4*]

RELVAR™ ELLIPTA™

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Please refer to the full Summary of Product Characteristics before prescribing

Trade Name: RELVAR ELLIPTA. **Active Ingredients:** 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). **Pharmaceutical Form:** 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Indications:** *The 92 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. *The 184 micrograms/22 micrograms dose:* for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate. **Dosage and Method of Administration:** *For Athsma:* One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta$_2$-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. *For COPD:* One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. **Contraindications:** *Hypersensitivity* to the active ingredient or excipients. **Precautions for Use:** Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. **Drug Interactions:** Beta-blockers, CYP3A4 inhibitors, P-glycoprotein inhibitors and sympathomimetic medicinal products (refer to the full Summary of Product Characteristics for list of drugs). **Fertility, Pregnancy and Lactation:** ***Pregnancy:*** No adequate data available. ***Lactation:*** insufficient information available. ***Fertility:*** There is no data in humans. Animal studies indicate no effect on fertility. **Effect on Ability to Drive or Use Machines:** No or negligible influence. **Undesirable Effects:** Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for complete list of undesirable effects). **Overdose:** There is no specific antidote. Treatment of overdose should consist of general supportive measures. **Local Presentations:** Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed. **Legal Category:** POM. **Marketing Authorisation Holder:** Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom **Marketing Authorisation Numbers:** EU/1/13/886/001-6 **DATE OF PREPARATION:** December 2013.

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

REPORTING ADVERSE EVENTS (AEs):

Malta & Gibraltar: **If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to:** GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131).

Malta: **alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:**

Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Gibraltar: **alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA):** https://yellowcard.mhra.gov.uk/

*Patients' current or previous maintenance inhalers: HandiHaler/ DISKUS/ MDI/ HFA (COPD); DISKUS/ MDI/ HFA (asthma).[4]

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MLT_GIB/RESP/0006/14 Date of preparation: January 2014

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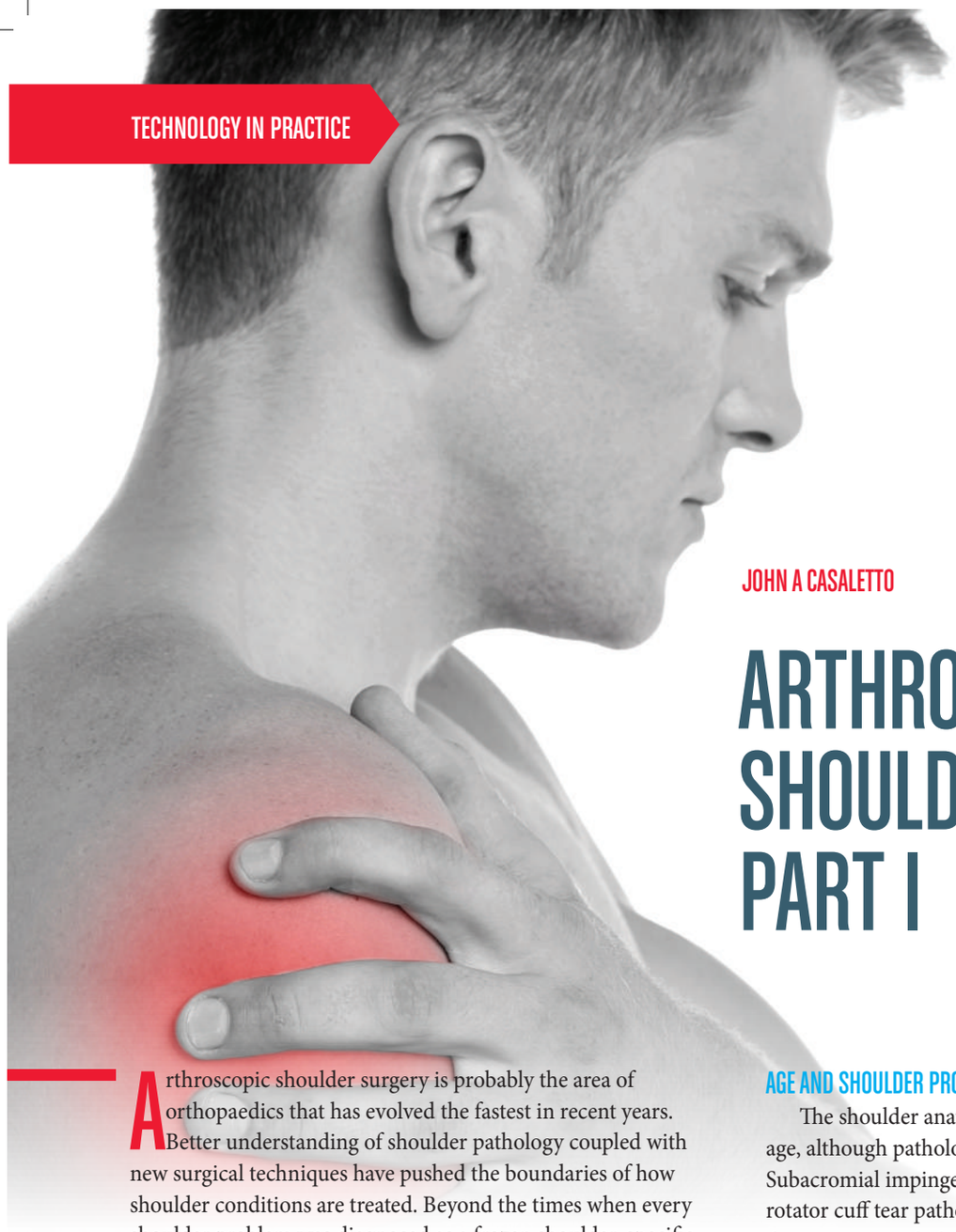
ISSUE GUIDE

TheSynapse



JOHN A CASALETTO

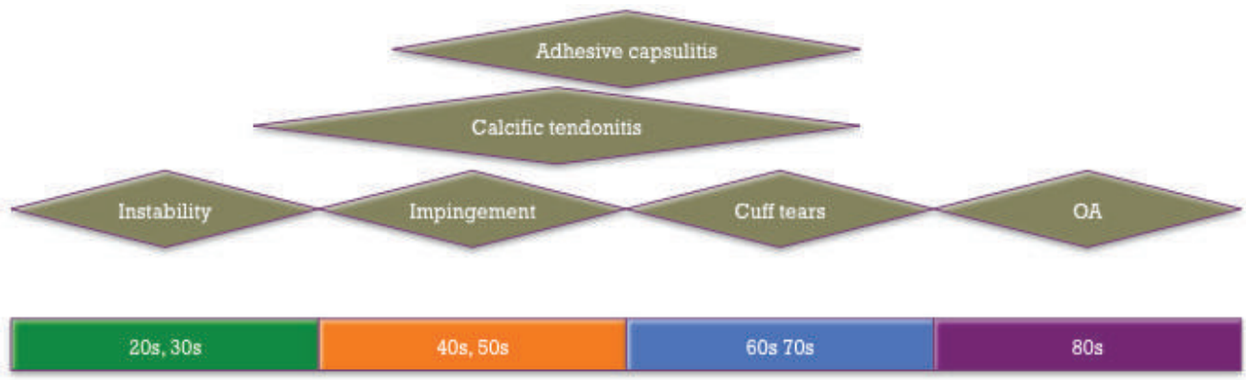
ARTHROSCOPIC SHOULDER SURGERY – PART I

Arthroscopic shoulder surgery is probably the area of orthopaedics that has evolved the fastest in recent years. Better understanding of shoulder pathology coupled with new surgical techniques have pushed the boundaries of how shoulder conditions are treated. Beyond the times when every shoulder problem was diagnosed as a frozen shoulder, specific pathologies are now easier to recognise and treat. Rotator cuff tears, sub-acromial impingement, calcific tendonitis, and arthritic and instability problems can all be addressed through the 'keyhole'.

AGE AND SHOULDER PROBLEMS

The shoulder anatomy lends itself easily to diagnosis by age, although pathologies can present in various shades of grey. Subacromial impingement is common in the 4th and 5th decade, rotator cuff tear pathology in the 6th and 7th decade, whilst degenerative pathology tends to present in the 7th and 8th decade. The guide in figure 1 is helpful in the differential diagnosis of shoulder pain. One would, for example, hesitate to make a diagnosis of subacromial impingement in an eighteen year old.

Figure 1: Commonest shoulder conditions by age.



SUBACROMIAL IMPINGEMENT IS COMMON IN THE 4TH AND 5TH DECADE, ROTATOR CUFF TEAR PATHOLOGY IN THE 6TH AND 7TH DECADE, WHILST DEGENERATIVE PATHOLOGY TENDS TO PRESENT IN THE 7TH AND 8TH DECADE

SUB-ACROMIAL IMPINGEMENT

This condition is primarily caused by impingement between the greater tuberosity and the undersurface of the acromion,[1] often giving rise to pain on the outer aspect of the shoulder joint radiating down to just above the elbow. Typically the pain is exacerbated by forward flexion and abduction and patients experience a painful arc of movement between 80-120 degrees. One often finds that the shoulder is less painful at maximum elevation unless the acromioclavicular joint is degenerate. Pain is reported to be worse at night with the patient unable to sleep on the affected shoulder.

The most common pathology causing impingement is a subacromial spur on the undersurface of the acromion, which decreases the subacromial space and impinges onto the rotator cuff and the long head of the biceps tendon. Impingement leads to bursal inflammation, tendonosis and eventually to tears in the rotator cuff. The pain arising from impingement and the subsequent restricted movement can lead to secondary frozen shoulder.

Neer's test can be carried out when the patient presents with a painful arc in abduction and forward flexion (Neer's sign), which is then relieved by injecting local anaesthetic into the subacromial space (Neer's test). In practice it is often more useful to give a corticosteroid and local anaesthetic injection into the subacromial space and check how response over the course of a few weeks.

Figure 2: Plain radiograph showing subacromial sclerosis and a large spur (blue arrow). The subacromial space is narrowed (by approximately half) suggestive of a rotator cuff tear. Coincidental acromioclavicular joint arthritis (orange arrow) is also seen in this film.

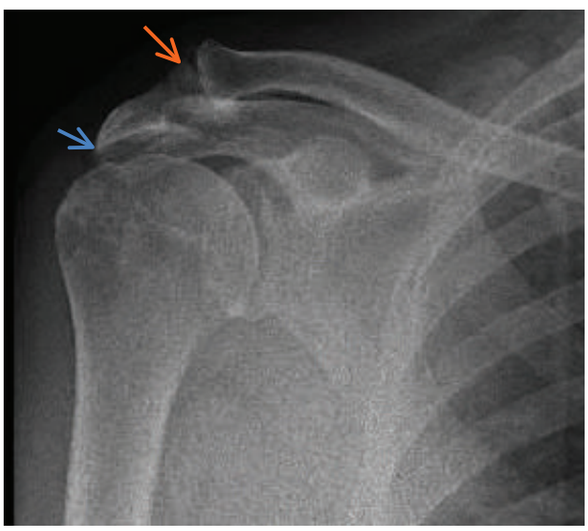
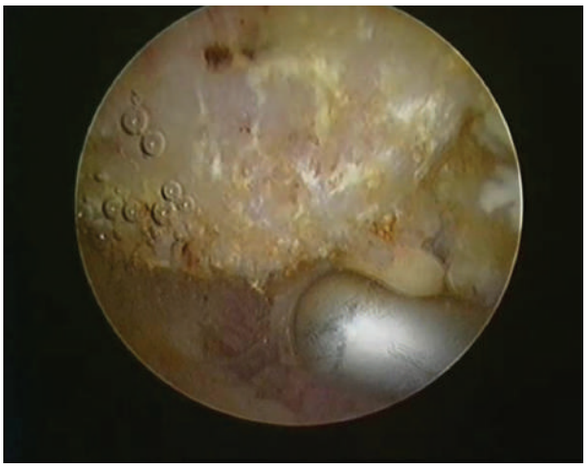


Figure 3: Arthroscopic view of the subacromial space showing a large subacromial spur which was uncovered after removing bursal tissue with the use of a radio-frequency ablator.



Plain radiography can show bony sclerosis or spur formation of the undersurface of the acromion and the greater tuberosity (figure 2).

In the early stages, the condition responds well to physiotherapy and corticosteroid injections. It is advisable to ensure that there is no tear of the rotator cuff as corticosteroid injections can lead to deterioration of the condition of the cuff which can affect future surgical repair.

Patients who have a significantly hooked acromion or a spur visible on X-ray tend to respond briefly or very poorly to non-surgical treatment but do well with arthroscopic subacromial decompression. The anterolateral acromial spur (figure 3) and the thickened bursa are removed using a radio-frequency ablator and an arthroscopic bone burr. Recovery from arthroscopic surgery is generally swift[2,3] with the majority of patients reporting decreased pain and markedly improved shoulder function within a few weeks of surgery.

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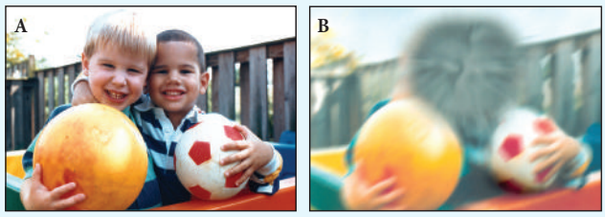
AGE-RELATED MACULAR DEGENERATION

JOHN GRECH HARDIE

Age-related Macular Degeneration (AMD) is a degenerative condition affecting the macular area of the retina. Those affected are usually over the age of 50 years and AMD is the leading cause of blindness over this age in the Western world. It results in distortion or loss of central sharp vision making it difficult to view the object of interest and to carry out close work, to read and write, to recognise faces and to drive although enough peripheral vision remains to allow other activities of daily life. Figure 1 compares a normal vision (a) and the vision in advanced AMD (b).

Figure 1: Comparison between a normal vision (A) and vision in advanced AMD (B)



Source - National Eye Institute, National Institutes of Health

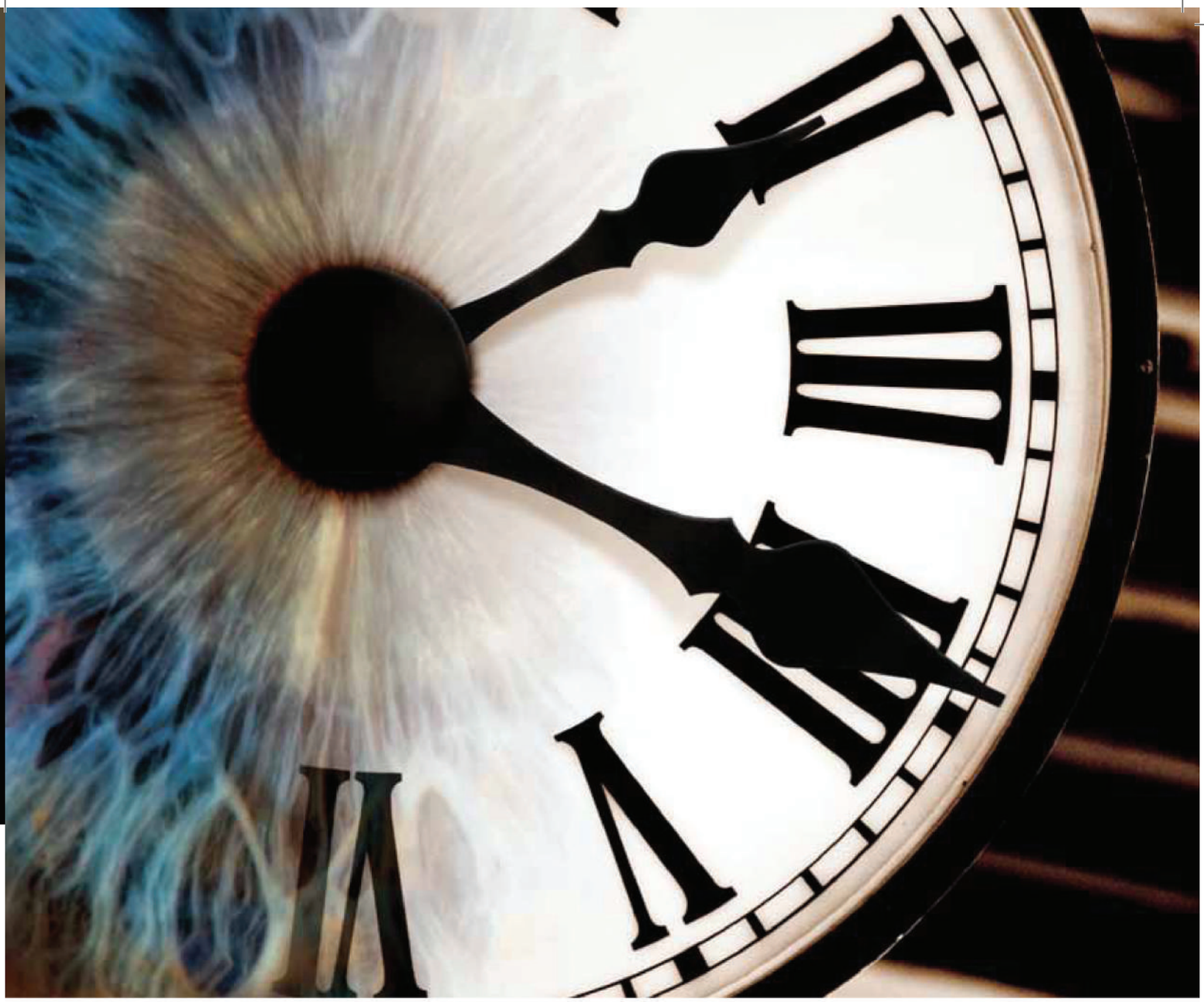
CAUSES AND RISK FACTORS

- Ageing: approximately 10% of people aged 66 to 74 show findings of macular degeneration. The prevalence increases to 30% in the 75 to 85 year age group.
- Family history: the risk of developing macular degeneration is 50% for those with a relative with macular degeneration versus 12% for those with no family history.
- Genetics: changes in several genes, the best studied of which are those involved with the complement system, have been implicated as possible risk factors in AMD.
- Hypertension.
- Cholesterol: elevated cholesterol may increase the risk of AMD.
- Obesity: a risk factor especially among men.
- Race: AMD is more common in Caucasians than in people of African descent.
- Exposure to sunlight especially blue light: there is conflicting evidence about this with some studies showing a relationship and others not.
- Smoking: tobacco smokers show a 2-3 times risk of AMD compared to non-smokers.

AMD is a gradually progressive disease and can pass from early AMD to geographic atrophy and/or neovascular AMD. Early AMD and geographic atrophy are the non-vascular or dry types and account for 90% of AMD while the neovascular or wet type accounts for 90% of blind registrations from AMD.

(A) EARLY AMD

Early AMD is usually asymptomatic with the appearance of Drusen of variable size and shape and focal hypo-pigmentation/ hyper-pigmentation of the macular area (figure 2). Drusen



It's time to slow the clock on the progression of **age-related macular changes**

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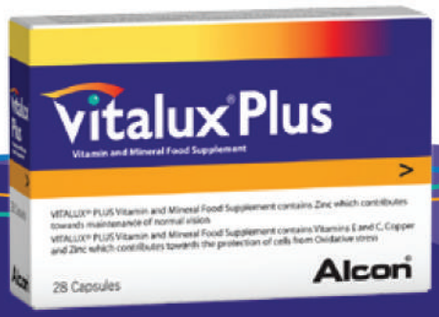


Alcon®

Figure 2: Early AMD

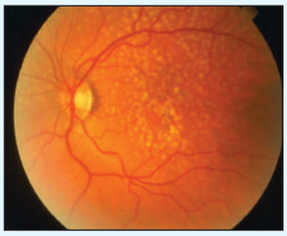


Figure 3: Amsler grid chart in advanced AMD

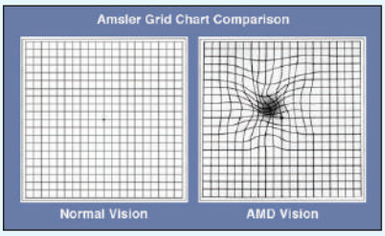


Figure 4: Geographic Atrophy

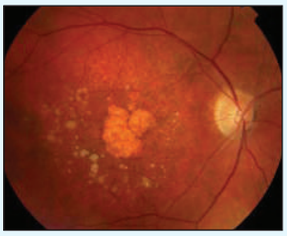
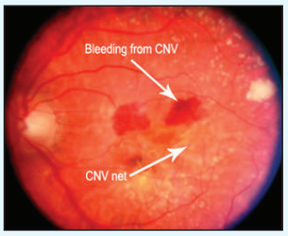


Figure 5: Neovascular AMD



Source - chicagoretinavitreous.com

are yellowish deposits or accumulations of PAS-positive amorphous material in Bruch's membrane under the retina while the pigmentary changes correspond to retinal pigment epithelium and photoreceptor loss.

Treatment at this stage involves:

- Stopping smoking: this is probably the most important modifiable factor.
- Diet and anti-oxidant vitamin supplementation: the Age-related Eye Disease studies (AREDS and AREDS2) showed that an anti-oxidant vitamin combination (500mg Vit C, 400IU Vit E, 15 mg beta-carotene, 80mg Zinc and 2mg Copper) had a moderate protective effect (25% decrease in the risk of developing late AMD) on the fellow eye of patients with vision loss from moderate to late AMD. Beta-carotene is contra-indicated in smokers as it increases the risk of lung cancer. AREDS2 showed that it can be substituted with 10mg lutein and 2mg zeaxanthin with no loss of effect and modern drug formulations make use of this fact. Many ophthalmologists place patients on these supplements even at an early stage of the disease.
- Monitoring of vision using an Amsler grid chart and yearly, or as required, ophthalmic review. An Amsler grid examines a person's central visual field. In the test, done serially at home, the subject looks at the small dot at the centre of the grid with each eye separately. The appearance of wavy or missing lines is indicative of macular disease and should prompt the patient to seek ophthalmic review. The test is particularly useful in monitoring the fellow unaffected eye of a patient with advanced AMD in the other eye. The chart can be easily downloaded from the Internet. Figure 3 depicts an Amsler grid chart in advanced AMD.

(B) GEOGRAPHIC ATROPHY

Together with Drusen, this shows slowly enlarging sharply demarcated areas of atrophy of the retina with exposure of the underlying choroidal vessels (figure 4).

Treatment at this stage is the same as for early AMD as well as the use of low-vision aides such as magnifying lenses and computer screen readers which enlarge reading material.

(C) NEOVASCULAR OR EXUDATIVE AMD

This typically presents with an acute change in central vision such as distortion (metamorphopsia) or a blind spot. The responsible lesion is a growth of choroidal neovascularisation (CNV) from the choroid through Bruch's membrane to a sub-RPE/retinal location. Clinically this appears as a greyish-green elevated lesion with associated leakage of blood (haemorrhage) and/or exudation (figure 5). The CNV grows and ultimately forms a central scar. Definitive diagnosis is achieved with intravenous fluorescein angiography. This defines the size and location of the lesion and any associated pigment epithelial detachment. Although invasive, the test is quick and quite harmless; apart from the remote possibility of allergy to the fluorescein dye. It is done on an out-patient basis and is also useful in follow-up after treatment.

Until recently treatment of neovascular AMD was not very effective in controlling the disease and preventing loss of vision. Previous treatments, now less commonly used, include:

- Laser treatment to ablate compact lesions away from the centre of the macula. This also destroys some surrounding healthy tissue leading to a blind spot.
- Photodynamic therapy which involves the intravenous injection of a drug, verteporfin, which selectively binds to growing new vessels in the eye. A specific laser is then shined into the eye to activate the drug which then causes the blood vessels to close off and regress.

With the introduction of **Anti-VEGF injection therapy** there is now hope in a previously hopeless situation. In neovascular AMD, abnormally high levels of vascular endothelial growth factor (VEGF) are secreted. This protein promotes the growth of abnormal new blood vessels. Anti-VEGF agents bind VEGF causing regression of the new vessels. This helps stabilise vision and in some cases restore some of the vision lost. The agents are injected directly into the vitreous of the eye and the injection is repeated monthly or bimonthly. The commonly used drugs are the approved but expensive ranibizumab (Lucentis®) and aflibercept (Eylea®) and the more commonly used and cheaper bevacizumab (Avastin®) used off-label. The duration of treatment varies in each case and may need to be long-term. This treatment is not a cure and the condition may progress in spite of this treatment. Ongoing stem cell research is beginning to show some promising results in the restoration of at least some of the vision lost in advanced cases of AMD.

INTRODUCING ONCE-DAILY SEEBRI BREEZHALER®

AN INHALED ANTICHOLINERGIC FOR PATIENTS WITH COPD.[4]

Seebri Breezhaler 44 micrograms inhalation powder, hard capsules

▼ This medicinal product is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION:
Each capsule contains 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium. The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 44 micrograms of glycopyrronium.

INDICATIONS:
Indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

DOSAGE:
The recommended dose is the inhalation of the content of one capsule once daily. Seebri Breezhaler is recommended to be administered, at the same time of the day each day. If a dose is missed, the next dose should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

CONTRAINDICATIONS: - Hypersensitivity to the active substance or to any of the excipients.

WARNINGS/PRECAUTIONS: - Seebri Breezhaler is not indicated for the initial treatment of acute episodes of bronchospasm. - Paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, Seebri Breezhaler should be discontinued immediately and alternative therapy instituted. - Caution in patients with narrow angle glaucoma or urinary retention. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Seebri Breezhaler and to contact their doctor imme diately should any of these signs or symptoms develop. - In patients with severe renal impairment including those with end stage renal disease requiring dialysis, Seebri Breezhaler should be used only if the expected benefit outweighs the potential risk. ☒ Seebri Breezhaler should be used with caution in patients with a history of cardiovascular disease. - Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. - There are no data from the use of Seebri Breezhaler in pregnant women. Glycopyrronium should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. - The use of glycopyrronium by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. - Glycopyrronium has no or negligible influence on the ability to drive and use machines.

INTERACTIONS: - The co administration of Seebri Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. - No clinically relevant drug interaction is expected when glycopyrronium is co administered with cimetidine or other inhibitors of organic cation transport.

ADVERSE REACTIONS: - Common (≥1/100 to <1/10): Nasopharyngitis, insomnia, headache, dry mouth, gastroenteritis, urinary tract infection. - Uncommon (≥ 1/1,000 to <1/100): Rhinitis, cystitis, hyperglycaemia, hypoaesthesia, atrial fibrillation, palpitations, sinus congestion, productive cough, throat irritation, epistaxis, dyspepsia, dental caries, rash, pain in extremity, musculoskeletal chest pain, dysuria, urinary retention, fatigue, asthenia, hypersensitivity, angioedema

LEGAL CATEGORY: POM

PACK SIZES: Single pack containing 30x1 hard capsules, together with one inhaler.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom.

MARKETING AUHORISATION NUMBER:
Seebri Breezhaler 44 micrograms inhalation powder, hard capsules - EU/1/12/788/001-006

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 22983217/21222872

2014-MT-SBR-1-JUL-2014

For information on Seebri Breezhaler dose expression, please refer to full prescribing information.

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Please see SPC for full prescribing information.

NOVARTIS

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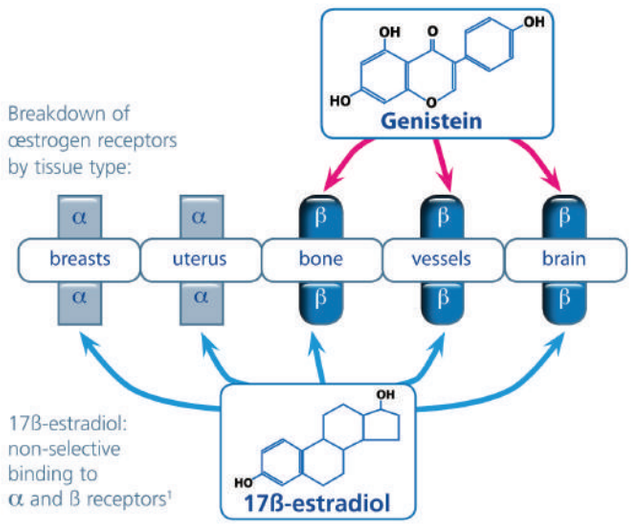
THE NEW 'ALTERNATIVE' FOR MENOPAUSE

MOIRA MIZZI

Plants have formed an integral part of our existence since time immemorial and since then we have been using them in many forms to support our survival. The use of plants or plant extracts for medicinal purposes has also been extensively explored and the intricacy of this research has followed the vertiginous progress in diagnostics and intervention. The use of synthetic chemicals for the cure of disease has nowadays taken up much of the pharmaceutical field; despite this, herbalism, or the study and use of plants as medicinals, is still a thriving facet of the pharma industry.

One of the medical fields in which herbalism is trying to establish a valid market is gynaecology, more specifically the menopause. Menopause is a highly particular phase in a woman's life that marks the end of fertility and slowly but determinedly steers her into middle and old age. It is a time of great physiological and psychological change which, if not tackled well, could lead to deleterious repercussions in both aspects. The hallmark of this biological havoc is a progressive

Figure 1: Comparison of the receptor selectivity between genistein and 17β-estradiol



decrease in the production of oestrogen by the ovaries which, if not corrected, could result in day-to-day inconveniences such as hot flushes, vaginal dryness, sleeping problems and mood swings to more serious consequences like osteoporosis and cardiovascular disease.

Replacing the depleted oestrogen is a natural solution to this predicament. For many decades, in fact, the rationale of the treatment for menopausal symptoms has hinged around oestrogen replacement, what is more commonly described as HRT or hormone replacement therapy, in the form of oral tablets, slow release subcutaneous administrations or local creams for vaginal dryness. Although their efficacy is close to optimal, even where the irritating day-to-day symptoms are concerned, the adverse events they can create can be quite hazardous especially where heart disease and breast cancer in susceptible individuals are concerned.

Complementary alternative medicines or CAMs have been a popular alternative or additive[1], especially in the United States[2,3], where at least 40% of the population uses a CAM at any

New

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soy isoflavones

Initial management of postmenopausal vasomotor disorders

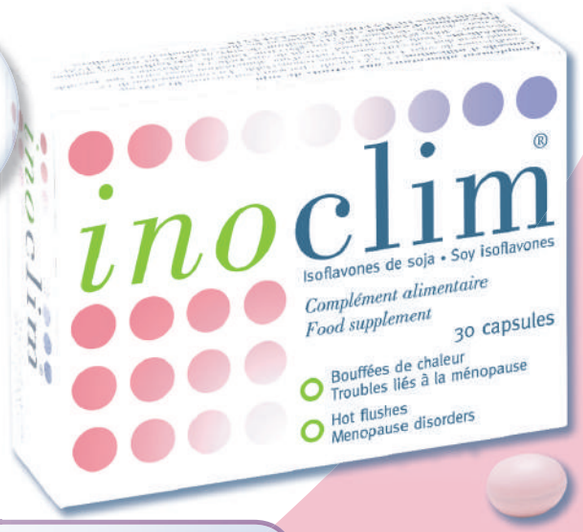
70% of postmenopausal women experience hot flashes(1)

Clinical effects of soy isoflavones supplement(1):

- Significant improvement of vasomotor disorders*
- No increase in endometrial thickness, breast density and vaginal cytology**

In postmenopausal women with distressing vasomotor disorders, initial management with isoflavones is reasonable(1)

40 mg soy isoflavones **per capsule**



- **Analytical quality control**
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- **3-month program. Renewable**

(1) According to NAMS 2011 Isoflavones Report. The role of soy isoflavones in menopausal health: report of the North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). Menopause. 2011;18(7):772-53.

* In 11/14 more recent randomized controlled trials (RCTs) evaluating the efficacy of isoflavones versus placebo in the treatment of postmenopausal vasomotor symptoms.

** Not recommended for women with personal or family history of breast cancer.

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one time or the other, with women over the age of 40 being the most avid users[4]. The publication of the results of the Women's Health Initiative randomised controlled trial in 2002[5], which highlighted a negative benefit-risk ratio with the prolonged use (5.2 years) of hormone therapy in older postmenopausal women also shifted the onus of popularity on the 'alternatives'. The CAMs most commonly used are herbal remedies and dietary phytoestrogens.

Herbal remedies come in various forms, including black cohosh, dong quai, ginseng, red clover and evening primrose oil. The most popular and the most studied herb is black cohosh whose medicinal use in gynaecology dates back to the Native Americans. Some clinical studies have found it effective in the treatment of hot flushes; however none of these trials have lasted more than six months and thus its efficacy in the long term is questionable[2]. Other clinical trials found no benefits when compared to placebo and in one trial[6], black cohosh appeared to be mostly effective in a subset of women with recent onset of menopause[3].

The identity of the active compounds of black cohosh are still unknown, and this presents an uncertainty both about its mode of action and its safety profile. Sadly, this is the dilemma faced with a number of herbal remedies launched on the market. The fact that most of the clinical trials are not placebo-controlled and only span a short period of time does nothing to help the situation[2].

Dietary phytoestrogens, extracted from a variety of food plants such as soy, beans and clover, are another alternative in the natural remedy repertoire. Interest in these products was sparked when high dietary intakes of soy was postulated to be one of the reasons of low incidence of menopausal symptoms in Japan, China and Korea. Composed of phenolic (rather than steroidal) compounds, these substances include chemicals such as isoflavones which when acted on by intestinal bacteria are converted from the conjugated to the unconjugated active forms such as genistein, daidzein and equol[2].

The mode of action of the isoflavones is clearer than their herbal counterparts. The oestrogen receptor is particular amongst the other steroid receptors in that it has the ability to bind with a wide range of molecules. It is made up of an α and a β counterpart - the α part of the receptor is responsible for breast and uterus while the β aspect controls bone, blood vessels and the brain (figure 1). The 17-β oestradiol molecule found in hormone replacement therapy is non-selective and this in fact results in the deleterious cardiac, uterine or breast side effects in susceptible individuals. Isoflavones, on the other hand have more affinity for the β-part of the receptor and thus is more selective to vasomotor, psychological and osteoporotic symptomatology[7].

Despite their promising mode of action, the niche for the isoflavone market seems to focus mostly on the vasomotor symptoms of menopause. 11 clinical trials have examined the use of isoflavones for hot flushes[2]; of these, only 3 out of 8 studies lasted more than 6 weeks and no particular efficacy was found even when used in moderately long term (24 weeks). Comparisons were not possible due to the different product, dosage and scoring systems used and the same beneficial effects were found both in the study and the placebo groups[2]. On the other hand, recent placebo-controlled double-blind studies showed promising results[8], and a 2012 systematic review and meta-analysis of randomized controlled trials concluded that soy isoflavone supplements are significantly more effective than placebo in the reduction of hot flashes.[9]

Omega-3-fatty acids have also been considered as a treatment for hot flushes and psychological distress, especially considering their recommendable safety profile and known beneficial cardiovascular effects[3]. Even if studies so far, have been encouraging[10], their role in menopausal women without overt psychological symptoms is still unknown.

Considering their popularity and widespread use, it is clear that despite their hazy clinical profile, complementary alternative medicines have found their place in the menopause community. I believe that better planned clinical trials with a larger number of participants and taking place over more extended timelines could yield more scientifically coherent data which would certainly support more their acceptance in the clinical scenario. After all, complementary, alternative or otherwise, harmonisation and standardisation of marketing protocols for all medicinals is the best way forward to transparency and accountability in the pharma industry.

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The Powerful Amoxicillin + Clavulanic Acid Combination

Forcid Solutab®:

- Contains amoxicillin and clavulanic acid in the ratio 7:1, the powerful combination to fight infections in unique Solutab® formulation

Forcid Solutab® indications:

- Acute bacterial sinusitis, acute otitis media, acute exacerbations of chronic bronchitis, community acquired pneumonia.
- Cystitis, pyelonephritis.
- Skin and soft tissue infections in particular cellulitis, animal bites.
- Severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Forcid Solutab® offers a convenient antibiotic therapy for adults and children:

- Easy and flexible administration, the unique versatile formulation can be swallowed intact or dissolved in water.
- Equally effective whether dissolved in water or taken as a tablet and rapidly absorbed.[1]
- Suitable for a wide range of patients: no sugar, no gluten, no sodium, no lactose.

Forcid Solutab® dosing in adults and children ≥ 40 kg:

- Standard dose of Forcid Solutab 1000 is 2 times a day.
- For infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections, Forcid Solutab1000 is recommended to be given 3 times per day.

Forcid® 1000 Abbreviated Prescribing Information. Presentation: Forcid® 1000, containing as active substances amoxicillin and clavulanic acid. Each tablet/dispersible tablet contains 875 mg amoxicillin as amoxicillin trihydrate and 125 mg clavulanic acid as potassium clavulanate. **Indications:** Amoxicillin/clavulanic acid tablets are indicated for the treatment of the following infections in adults and children: acute bacterial sinusitis (adequately diagnosed), acute otitis media, acute exacerbations of chronic bronchitis (adequately diagnosed), community acquired pneumonia, cystitis, pyelonephritis, skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis, bone and joint infections, in particular osteomyelitis. Consideration should be given to official guidance on the appropriate use of antibacterial agents. **Duration of therapy:** The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review. **Posology:** The dose of amoxicillin/clavulanic acid that is selected to treat an individual infection should take into account the expected pathogens and their likely susceptibility to antibacterial agents, the severity and site of infection, the age, weight and renal function of the patient. **Adults and children over 40 kg:** The standard dose of Forcid 1000 is 2 times a day. For infections such as otitis media, sinusitis, lower respiratory infections and urinary tract infections, Forcid 1000 is recommended to be given 3 times per day. **Children under 40 kg:** 25mg/3.6mg/kg/day to 45mg/6.4mg/kg/day given as 2 divided doses. No clinical data are available for amoxicillin/clavulanic acid 7:1 formulations higher than 45mg/6.4mg/kg per day in children under 2 years. There are no clinical data for amoxicillin/clavulanic acid 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population cannot be made. **Elderly patients:** No dose adjustment is necessary. **Patients with impaired renal function:** No dose adjustment in dose required in patients with creatinine clearance (CrCl) greater than 30ml/min. In patients with CrCl less than 30ml/min, use of Forcid 1000 is not recommended as no recommendations for dose adjustments are available. **Patients with impaired liver function:** Dose with caution and monitor hepatic function at regular intervals. **Method of administration:** Amoxicillin/clavulanic acid tablets are for oral use. Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption. Forcid tablets can be swallowed whole with a glass of water, or first dissolved in a ½ cup of water (at least 30ml) and stirred thoroughly before swallowing. **Contraindications:** Hypersensitivity to the active substances, to any penicillins or to any of the excipients. History of severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam). History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid. **Special warnings and precautions for use:** Before initiating therapy, careful enquiry should be made of previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents. Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in patients with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid must be discontinued and appropriate alternative therapy instituted. If an infection is proven to be due to amoxicillin-susceptible organism(s), consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance. This presentation of amoxicillin/clavulanic acid is not suitable for use when there is high risk that presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should also not be used to treat penicillin-resistant *S. pneumonia*. Convulsions may occur in patients with impaired renal function or in those receiving high doses. Avoid if infectious mononucleosis is suspected. Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. Prolonged use may result in overgrowth of non-susceptible organisms. Occurrence of feverish generalised erythema associated with pustula at treatment initiation may be a symptom of acute generalised exanthemous pustulosis (AGEP) and requires treatment discontinuation and contra-indicates any subsequent administration of amoxicillin. Use with caution in patients with evidence of hepatic impairment. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects. Antibiotic-associated colitis has been reported, consider in patients who present with diarrhoea. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation. Periodic assessment of organ system functions is advisable during prolonged therapy. Prolongation of prothrombin time was reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation. In patients with renal impairment, dose should be adjusted according to degree of impairment. In patients with reduced urine output, crystalluria has been observed very rarely, mainly with parenteral therapy. Maintain adequate fluid intake and urinary output during administration of high doses of amoxicillin to reduce possibility of amoxicillin crystalluria. If bladder catheter is in-situ, check patency. False positive results may occur when testing presence of glucose in urine with non-enzymatic methods during treatment of amoxicillin; use enzymatic glucose oxidase methods. Clavulanic acid in Forcid may cause non-specific binding of IgG and albumin by red cell membranes leading to false positive Coombs test. Reports of positive test results using Bio-Rad Laboratories Platelia *Aspergillus* EIA test; cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported; positive results should be interpreted cautiously and confirmed by other diagnostic methods. Forcid 1000 contains 0.64 mmol potassium per tablet (25 mg). **Pregnancy and lactation:** Use in pregnancy should be avoided unless considered essential by physician. Both amoxicillin and clavulanic acid are excreted in breast milk; consequently diarrhoea and fungus infection of mucous membranes is possible in breast-fed infants. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by physician in charge. **Undesirable effects:** The most commonly reported adverse reactions (ADRs) are diarrhoea, nausea and vomiting. For a full listing of undesirable effects, refer to the complete Summary of Product Characteristics for Forcid® 1000. Marketing authorization holder: Astellas Pharma Europe BV., Sylviusweg 62, 2333 BE Leiden. The Netherlands. 13-FOR-003 Adverse events should be reported to the local regulatory authority and Astellas Pharma Europe BV., Sylviusweg 62, 2333 BE Leiden. The Netherlands. Please read carefully the instructions on the package leaflet. 13-FOR-004 102013

Reference: 1. H. Sourgens et al. International Journalof Clinical Pharmacology and Therapeutics. 2004; 42: 165-173.

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CHERYL KAYE CACHIA

MY EXPERIENCE IN THE MMSA

Over the years, the Maltese public has grown familiar with the Malta Medical Students' Association (MMSA), particularly through the outreaches and health checks which it conducts during various events, especially those held annually in Valletta such as the World Diabetes Day in November. However, to us medical students the MMSA is much more than just that.

First and foremost it is a platform which enables us students to actively participate in the academic system in order to better our own medical education. Year in, year out, the MMSA's Standing Committee on Medical Education (SCOME) organizes workshops and seminars in order to compliment the medical curriculum by focusing on particular skills and competencies. For my part, one of the most interesting workshops I participated in was the *Practice Makes Perfect* workshop which focused on hands-on skills such as suturing and bandaging.

The MMSA also provides us with the opportunity to gain experience in various aspects of the public health sector through its Standing Committee on Public Health (SCOPH). Personally, this is one of my favourite facets of our organisation. From our very first year as medical students we start getting into contact with the general public and are able to contribute back to our society by putting our knowledge into practice. Throughout these past two years, I have participated in numerous public health checks and have helped raise public awareness on topics ranging from cardiovascular disease and stroke prevention to antibiotic use and organ donation.

Last but not least, the MMSA also offers its members the opportunity to go on international student exchanges. Arguably, this is one of the most exciting aspects of our beloved organisation. Luckily, this summer I was chosen to go on a professional student exchange to Finland. During my month-long venture in the Clinical Microbiology Department at Kuopio University Hospital I got acquainted with a totally different healthcare system to that in Malta. Such an experience is very mind-opening and enables one to meet medical students from other countries and make new contacts abroad.

QUIZ

THE EDITORIAL TOOK YOU FOR A WALK DOWN THE MEMORY LANE ... WHO CARRIED OUT THE FIRST HUMAN HEART TRANSPLANT?

THE 5TH CORRECT ENTRY WILL WIN A MEDICAL LANGUAGE TRANSLATOR BOOK PUBLISHED BY MMSA.

THE COMPETITION IS OPEN TO ALL DOCTORS, DENTAL SURGEONS & PHARMACISTS, AS WELL AS STUDENTS OF THESE PROFESSIONS. GOOD LUCK!

SEND YOUR ANSWERS BY 30TH NOVEMBER TO IAN.C.ELLUL@GMAIL.COM

QUIZ WINNER

WINNER OF THE MEDICAL LANGUAGE TRANSLATOR BOOK PUBLISHED BY MMSA

DR SHIRLEY FARRUGIA MD MSC HSM DIP IMC (RCS ED) MMCFD IS THE LUCKY WINNER OF THE MEDICAL LANGUAGE TRANSLATOR BOOK PUBLISHED BY MMSA. SHE WAS THE 5TH PARTICIPANT WHO REPLIED CORRECTLY TO THE QUESTION, 'LAST AUGUST, 8 STUDENTS FROM THE MALTA MEDICAL STUDENTS' ASSOCIATION (MMSA) JOURNEYED TO WHICH COUNTRY TO REPRESENT MALTA IN THE INTERNATIONAL FEDERATION OF MEDICAL STUDENTS ASSOCIATION (IFMSA) 63RD GENERAL ASSEMBLY AUGUST MEETING?' THE CORRECT ANSWER WAS TAIPEI, TAIWAN.

A laugh a day keeps the doctor away

MULTIPLICATION LESSONS

There was once two doctors who had been married for more than 60 years. They shared everything. They talked about everything. Nothing was held back. Well … almost nothing ...

They had kept no secrets from each other except that the frail old female doctor had a shoe box in the top of her closet that she had cautioned her husband never to open or ask her about.

For all of these years, he had never thought about the box, but one day his wife got very sick and the doctor said she would not recover.

In trying to sort out their affairs, the old man took down the shoebox and took it to her bedside. She agreed that it was time that he should know what was in the box.

When he opened it, he found two crocheted doilies and a stack of money totaling €5,000 (in €5 notes). He asked her about the contents.

"When we were to be married," she started, "my grandmother told me that the secret of a happy marriage was to never argue. She told me that if I ever got really angry with you, I should just keep quiet and crochet a doily."

The old man was so moved, he had to fight back tears. Only two precious doilies were inside the box! She had only been really angry with him two times in all those years of living and loving. He almost burst with happiness. "Honey," he said, "that explains the doilies, but ... what about all this money? Where did it all come from?"

"Oh," she said, "that's the money I made from selling the doilies."

30 OCTOBER 2014	THURSDAY 30 OCTOBER 2014 Managing Quality in Project Management
10 NOVEMBER 2014	MONDAY 10 - WEDNESDAY 12 NOVEMBER 2014 Dealing with Self Harm
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OMEPRAZOLE-INDUCED DELIRIUM

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INTRODUCTION

Delirium is a common manifestation in the elderly, with studies quoting a prevalence of up to 14% in the community in those aged 85 years and older.[1] It occurs in 10-34% of patients living in long term care facilities,[2] and occurs in 30% of patients presenting to the accident and emergency departments.[3] Despite the fact that 10-42% suffer from delirium during a hospital stay, complicating 17-61% of major surgical procedures, it is unfortunately only recognized in 20-50% of cases.[1,4] Despite the higher prevalence in the elderly population, it may present in all age groups, identified as per the 'American Psychiatric Association' (APA) Diagnostic and Statistical Manual (DSM-IV-TR and DSM-V Proposed Revision) criteria (Table 1).[5]

Table 1: Diagnostic and statistical manual criteria (DSM-IV-TR and DSM-V).[5]

- Altered consciousness with inattention difficulties
- Cognitive or perceptual disturbances (unrelated to dementia)
- Acute onset of symptoms (hours to days), typically fluctuating in nature
- History, clinical assessment and investigations suggestive of organic causes for symptoms (including medication)

Medications are potential causes for delirium, accounting for as much as 39% of cases of delirium in the elderly, with the latter population being more at risk than other age groups due to altered pharmacokinetic and pharmacodynamics associated with the aging process.[6]

Proton pump inhibitors (PPIs) in particular are known to cause neuropsychiatric symptoms. One such PPI is omeprazole, a racemic mixture of two active enantiomers, classified as an inhibitor of the H+/K+-ATPase found on gastric parietal cells.[7] Omeprazole-induced delirium has been documented in literature. One study on a small subgroup of cancer patients documented that histamine receptor 2 antagonists, also used as a treatment for gastritis, were more commonly associated with delirium than PPIs.[8] That said, such cases have all been associated with metabolic and electrolyte disturbances, most notably hyponatremia and hypomagnesemia.[7,9] We would like to report a case of omeprazole-induced delirium which clearly correlates with the time of its administration and omission. To our knowledge, this is the first case to document such a causal relationship without any other causes of delirium such a PPI-induced electrolyte disturbances.

CASE REPORT

An eighty-five year old gentleman was admitted under surgical care because of a possible upper gastrointestinal (GI) bleed. He was previously well, with no relevant past medical history and fully independent prior to admission. On initial assessment at the emergency department, he was alert and oriented, haemodynamically stable and neurologically intact. In view of his severe epigastric pain, he was started on 40mg twice a day of intravenous omeprazole (Losec®), a proton-pump inhibitor, as part of the standard management protocol, which was later given as tablets. Twelve hours later, the patient appeared to be acutely confused, delirious and uncooperative. These symptoms got progressively worse during his admission. A collateral history from his relatives did not reveal any remarkable evidence of erratic alcohol or other drug dependence. Physical examination was unremarkable.

The patient was inattentive and incoherent, and thinking was clearly disorganised, with an altered level of consciousness manifesting itself as hyperactivity, reported by various nursing personnel. These symptoms were acute in onset and fluctuating. The acute fluctuating cognitive disturbance with the impression that the cause of the symptoms was organic in origin supported the diagnosis of delirium as per the Assessment Method (CAM) and APA DSM-IV-TR and DSM-V diagnostic criteria.[5,6]

Investigation of his epigastric pain did not reveal evidence of any acute GI bleeding and a diagnosis of probable gastritis was made. However, the persistence of delirium beyond the initial few days of admission prompted further investigations (Table 2)[5] in order to identify any possible contributing factor towards the delirium, including electrolyte disturbances, metabolic disorders, sepsis, hypoxia, constipation, organ failure, and hypoxia, amongst others.[10]

Brain computer tomography (CT) scan and Electroencephalogram (EEG) are most often recommended to exclude acute (which need immediate management) or chronic intracranial pathologies such as a cerebrovascular event or a newly diagnosed space-occupying lesion. Despite them being used to identify or confirm specific diagnoses, thereby allowing a clinician to manage the patient accordingly, one should keep in mind that both CT and EEG have very high false negative (17%) and false positive (22%) rates. One should therefore understand that further tests such as magnetic resonance imaging (MRI) may be needed if there is a diagnostic suspicion, even if results are initially normal. That said, one would expect a higher diagnostic yield with CT in patients with focal neurological deficits.[11] The CT scan revealed only an element of brain atrophy, which was thought to be consistent with this patients' age. There was no evidence of acute infarction or any brain pathology.

Table 2: Basic investigations for diagnosing cause for delirium.[5]

Blood Tests
- Complete blood count
- Electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphate, iron profile)
- Liver function tests including bilirubin, albumin, liver enzymes, ammonia
- Endocrine investigations including thyroid function tests, folate, vitamin B12
- Blood glucose
- Blood cultures
- Arterial Blood Gases (for Hypoxia and Hypercapnia)
- Toxicology
- Inflammatory markers including Estimated Sedimentaiton Rate (ESR), C-reactive protein (CRP), ferritin

Urine Tests
- Urinalysis
- Urine Cultures

Neuroimaging
- CT Brain
- Electroencephalography

Others
- CSF Analysis (Biochemistry and Cytology)
- ECG
- Pulse Oximetry
- Chest X-Ray
- Abdominal X-Ray

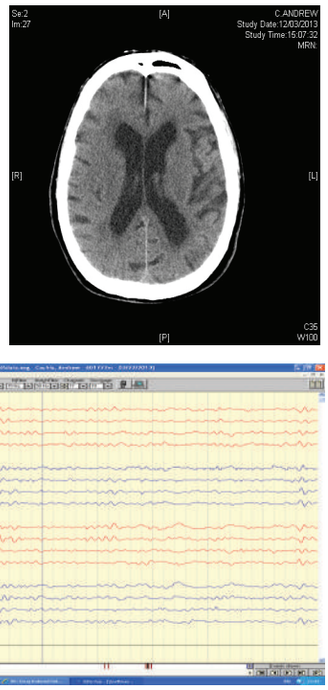
The background EEG showed a generalised slowing of the background rhythm with no focal or epileptiform features, consistent with a non-specific encephalopathy (Figure 1).

This patient was not started on any medication, other than omeprazole during his hospital stay, and therefore the possibility of a drug-induced delirium was not considered immediately. However, as a last attempt, the omeprazole was stopped and he was given ranitidine instead for his GI symptoms. Twelve hours later, the patient was back to his pre-morbid state, fully oriented, talkative, independent and co-operative with doctors and paramedical staff. After an 8 day hospital stay, he was discharged.

CONCLUSION

Despite the fact that 48% of patients report adverse effects secondary to omeprazole ingestion, only a very small minority complain of neurological symptoms, the majority of which being headaches (3% of total side-effects).[8] Neuropsychiatric symptoms including delirium have been reported in the literature[9] and are also documented in the product literature. The summary of product characteristics (for Losec®)[12] acknowledges that psychiatric symptoms including delirium can occur rarely, secondary to severe hypomagnesaemia in patients treated with proton pump inhibitors for at least 3 months. Case reports also report delirium secondary to hyponatremia

Figure 1: EEG showing non-specific slowing of the background rhythm and CT scan of the brain showing generalised atrophy.



in patients treated with proton pump inhibitors for at least 3 months.[13] Notwithstanding this fact, the authors conducted a thorough literature search and did not find any case of documented omeprazole-induced delirium whereby sodium and magnesium levels are normal. In conclusion, physicians should not undervalue the possibility of documented omeprazole-induced non-organic psychosis. Earlier recognition and prompt cessation of the drug will avoid unnecessary investigations as well as reduce the length of hospital stay.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

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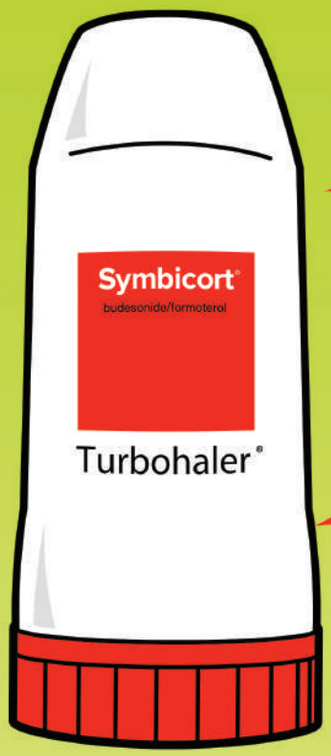

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Symbicort 100/6 is not appropriate for patients with severe asthma. **COPD (Symbicort 200/6; 400/12):** Symptomatic treatment of patients with severe COPD (FEV1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators. **Dosage and Administration: Asthma (Symbicort maintenance therapy – regular maintenance treatment with a separate rescue medication): Adults *(including elderly)* 100/6 and 200/6:** 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily; **400/12:** 1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily ***Adolescents (12-17 years)*** **100/6 and 200/6:** 1-2 inhalations twice daily; **400/12:** 1 inhalation twice daily. ***Children 6 years and older*** **100/6 only**: 2 inhalations twice daily. ***Symbicort is not recommended for children under 6 years. Symbicort 400/12 is not recommended for children under 12 years.*** Not intended for the initial management of asthma. Dose should be individualised. If an individual patient requires dosages outside recommended regimen, appropriate doses of β_2 adrenoceptor agonist and/or corticosteroid should be prescribed. When long-term symptoms are controlled, titrate to the lowest effective dose, which could include a once daily dosage. **Asthma (Symbicort maintenance and reliever therapy – regular maintenance treatment and as needed in response to symptoms)** ***for Symbicort 100/6 and 200/6 only (NOT recommended with 400/12 strength):*** especially consider for (i) patients with inadequate asthma control and in frequent need of reliever medication (ii) patients with asthma exacerbations in the past requiring medical intervention. Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Symbicort as-needed inhalations. ***Adults (including elderly) 100/6 & 200/6:*** 1 inhalation twice daily or as 2 inhalations once daily. For some patients a dose of 2 inhalations twice daily may be appropriate (200/6 strength only). Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is not normally needed; however, up to 12 inhalations a day could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice and should be reassessed; their maintenance therapy should be reconsidered. Patients should be advised to always have Symbicort for reliever use. ***Children and adolescents under 18 years of age:*** not recommended. **COPD (200/6):** ***Adults:*** 2 inhalations twice daily. **(400/12):** 1 inhalation twice daily. **Contraindications, Warnings and Precautions etc.:** ***Contraindications:*** Hypersensitivity (allergy) to budesonide, formoterol or lactose (which contains small amounts of milk proteins). ***Warnings and Precautions:*** If treatment is ineffective, or there is a worsening of the underlying condition, therapy should be reassessed. Sudden and progressive deterioration in control requires urgent medical assessment. Patients should have their appropriate rescue medication available at all times, i.e. either Symbicort or a separate reliever. If needed for prophylactic use (e.g. before exercise) a separate reliever should be used. Therapy should not be initiated during an exacerbation. Serious asthma-related adverse events and exacerbations may occur and patients should continue treatment but seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of Symbicort. Paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. This responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. As with any inhaled corticosteroid, systemic effects may occur, particularly at high doses prescribed for long periods. These may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract and glaucoma and more rarely a range of psychological or behavioral effects. Potential effects on bone should be considered especially in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly. During transfer from oral steroid therapy to Symbicort, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms which will need treatment. In rare cases, symptoms such as tiredness, headache, nausea and vomiting can occur due to insufficient glucocorticosteroid effect and temporary increase in the dose of oral glucocorticosteroids is sometimes necessary. Observe caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, or severe cardiovascular disorders. As with other β_2 adrenoceptor agonists, hypokalaemia may occur at high doses. Particular caution recommended in unstable or acute severe asthma as this effect may be potentiated by xanthine-derivatives, steroids, diuretics and hypoxia. Monitor serum potassium levels. Hypokalaemia may increase the disposition towards arrhythmias in patients taking digitalis glycosides. In diabetic patients, consider additional blood glucose monitoring. Symbicort contains lactose monohydrate, as with other lactose containing products the small amounts of milk proteins present may cause allergic reactions. Interactions: Concomitant treatment with potent CYP3A4 inhibitors should be avoided. If this is not possible the time interval between administration should be as long as possible. Symbicort maintenance and reliever therapy is not recommended in patients using potent CYP3A4 inhibitors. Not to be given with beta adrenergic blockers (including eye drops) unless there are compelling reasons. Concomitant administration with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), MAOIs and TCAs can prolong the QTc-interval and increase the risk of ventricular arrhythmias. L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance. Concomitant administration with MAOIs, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertension. Risk of arrhythmias in patients receiving anaesthesia with halogenated hydrocarbons. Concomitant use of other beta adrenergic drugs or anticholinergic drugs can have a potentially additive bronchodilating effect. **Pregnancy and Lactation:** Should only be used when the benefits outweigh the potential risks. Budesonide is excreted in breast milk, however at therapeutic doses no effects on the child are anticipated. **Undesirable effects:** ***Common:*** headache, palpitations, tremor, candida infections in the oropharynx, coughing, mild irritation in the throat, hoarseness. ***Uncommon:*** tachycardia, nausea, dizziness, bruises, aggression, psychomotor hyperactivity, anxiety, sleep disorders. ***Rare:*** hypokalaemia, cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles, bronchospasm and immediate and delayed hypersensitivity reactions including exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction. ***Very Rare:*** psychiatric disorders including depression, behavioural changes (predominantly in children), angina pectoris, prolongation of QTc-interval, hyperglycaemia, taste disturbance, Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma and variations in blood pressure. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. **Package Quantities:** Each Symbicort Turbohaler 100/6 or 200/6 contains 120 inhalations. Each Symbicort Turbohaler 400/12 contains 60 inhalations. **Legal Category:** Prescription Only Medicine (POM). **Marketing Authorisation Number(s):** MA 046/00901-3. **Marketing Authorisation Holder (MAH):** AstraZeneca AB, Gartunavagen, S-151 85 Sodertalje, Sweden. **Further product information available on request from:** Associated Drug Company Limited, Triq l-Esportaturi, Mriehel, Birkirkara BKR 3000, Malta. Telephone: (+356) 22778000. Fax: (+356) 22778120. **Abridged Prescribing Information prepared:** 04/12. Symbicort and Turbohaler are Trade Marks of the AstraZeneca group of companies. URN: 13/0125 **Date of Preparation:** October 2014.

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COMMUNICATING ABOUT CARDIOPULMONARY RESUSCITATION AND DO NOT ATTEMPT RESUSCITATION DECISIONS

CARL TUA

ABSTRACT

As the boundaries of medicine are pushed, and life prolonged further, it is increasingly evident that healthcare and modern medicine no longer simply equate to a prolongation of life at all costs; actually, decisions not to attempt cardiopulmonary resuscitation (CPR) may be in a patient's best interests. This article discusses how we discuss these complex decisions with those affected by them: our patients.

INTRODUCTION

Healthcare is not simply about prolonging one's life at all costs. When respiratory or cardiac arrest is part of the expected process of dying, then, not attempting cardiopulmonary resuscitation (CPR) is in the patients' best interests, allowing them to die with dignity and peacefully. Yet reports of poorly made decisions about CPR have appeared in the international press and receive much attention from the general public.[1] Prompted by these reports, guidelines were released by the British Medical Association, the Resuscitation Council (UK) and the Royal College of Nursing in 2001, and these are updated regularly. These give guidance on various ethical and legal principles governing CPR.[2] One of these key principles is the paramount importance of communication and provision of information to the patient and family. However these conversations may be fraught with difficulty for healthcare providers, patients and families, making some doctors reluctant to address the issue. Yet the importance of decisions relating to CPR mean that, despite their complexity and sensitivity, open and frank communication between the healthcare team and patient is essential.

COMMUNICATING ABOUT CPR WITH PATIENTS

The first step lies in ascertaining whether the patient wishes to discuss CPR or not. Patients approaching the end of their life may have directly or indirectly indicated that they are not interested in having this discussion; therefore burdening them with discussions on interventions from which they will obviously not benefit is needless. The amount of involvement a patient has in these discussions should be tailored to fit their indicated desires.

Dunn et al.[3] outline the key aspects of a discussion on CPR:

- Discussing the current medical condition, including information on prognosis and disease progression;
- Eliciting goals and values for care;
- Discussing CPR in a manner that adheres to criteria for informed consent.

The value of performing CPR is greatly dependent on the physical condition and underlying disease process, but while the doctor may be aware of the medical status of a patient, for a variety of reasons, including their own wishes, the patient may be less well-informed. However, someone who is unaware of the prognosis cannot adequately discuss CPR, as that individual is unable to balance the probable outcomes with or without CPR. A conversation about CPR and do not attempt resuscitation decisions (DNARs) should be a discussion of patient goals, quality of life, and what treatments are most likely to achieve these. Goals change with time and illness so discussions about goals of treatment should be done throughout the duration of the patient's life-limiting disease and not simply at the very beginning, or during the final dying process. Early on in the

course of a life-limiting disease the aim of treatment may be to prolong life enough to see the birth of a granddaughter or nephew, while further on during the course of this disease the aim may be to spend the final hours at home surrounded by family.

Patients often fear the loss of control that might occur in the final phases of their life. Advanced care planning gives patients a sense of control and ensures that their wishes are followed even if they become incompetent.[4] Patients should be given honest answers regarding the practical aspects of CPR and treatment post-CPR, but this should be given at a level the patient understands. It may be easy to get sidetracked into discussing unimportant medical technicalities, which may easily lead to misunderstandings; yet information should never be withheld simply because this is too complex or difficult for the healthcare team to explain adequately.[4-5] It should be clear to the patient that offering an intervention, such as CPR, does not necessarily mean that the doctor thinks that it will work and that it is the right thing to do. It should be clear that refusing such intervention is an equally valid choice. Cases popularized in the media, or past experience with family members may have resulted in specific concerns about both under-treatment, and poor outcomes after cardiac arrest such as a persistent vegetative state. It is important to try and understand the basis of these concerns and explain them appropriately. For example, patients may not wish to be put on ventilators because "they may never wake up"; this should prompt a discussion on non-initiation of treatment or withdrawal of treatment, as this patient may wish to have a trial of invasive ventilation but would not wish to be ventilated indefinitely.[6]

Maltese legislation does not provide any reference to the concepts of CPR, DNARs and living wills. As such, determination of CPR status remains a clinical decision based on the professional capacity of the clinician in charge, taking into consideration the socio-cultural background of the patient.

WHERE ARE WE FAILING PATIENTS?

Yuen et al.[7] suggested that problematic DNARs often failed in one or more of four areas:

- Discussions held too infrequently, with patient preferences being neglected;
- DNAR discussions delayed until it is too late for the patient to participate;
- Inadequate information to facilitate informed decisions;
- Inappropriate extrapolation of DNAR to other treatments.

Three of these areas relate directly to communication with patients, further underlining its importance. These are not problems of technology, lack of equipment or even finances, but a medico-cultural framework that has resulted in inadequate communication by healthcare providers.

CONCLUSION

Despite evidence showing that patient priorities for end-of-life care include consistent, reliable medical advice and avoiding inappropriate prolongation of the process of dying, the medical establishment often persists with a cure-driven culture and for various reasons is often reluctant to engage the patient in an informed discussion on prognosis, values and goals of care, and CPR. A discussion between all healthcare providers on how we have failed to communicate with patients and families at the end of life is required before we can start to improve our communication with our patients.[3]

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions. **PRESENTATION:** Each capsule contains 143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). Ultibro Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis it should be used only if the expected benefit outweighs the potential risk. Ultibro Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. There are no data available for the use of Ultibro Breezhaler in patients with severe hepatic impairment, therefore caution should be observed in these patients. There is no relevant use of Ultibro Breezhaler in the paediatric population (under 18 years) in the indication COPD. The safety and efficacy of Ultibro Breezhaler in children have not been established. No data are available. Method of administration For inhalation use only. The capsules must not be swallowed. The capsules must be administered only using the Ultibro Breezhaler inhaler. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the other excipients. **WARNINGS/PRECAUTIONS:** Ultibro Breezhaler should not be administered concomitantly with medicinal products containing other long acting beta adrenergic agonists or long acting muscarinic antagonists, the pharmacotherapeutic groups to which the components of Ultibro Breezhaler belong. Asthma: Ultibro Breezhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long acting beta2 adrenergic agonists may increase the risk of asthma related serious adverse events, including asthma related deaths, when used for the treatment of asthma. Not for acute use: Ultibro Breezhaler is not indicated for the treatment of acute episodes of bronchospasm. Hypersensitivity related to indacaterol Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of Ultibro Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, treatment should be discontinued immediately and alternative therapy instituted. ***Paradoxical bronchospasm:*** In clinical studies with Ultibro Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted. *Narrow-angle glaucoma:* No data are available in patients with narrow angle glaucoma, therefore Ultibro Breezhaler should be used with caution in these patients. Patients should be informed about the signs and symptoms of acute narrow angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. *Urinary retention:* No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of $beta_2$ adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to $beta_2$ adrenergic agonists. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine. ***Pregnancy and Lactation:*** There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two components. Beta adrenergic blockers may weaken or antagonise the effect of $beta_2$ adrenergic agonists. Therefore Ultibro Breezhaler should not be given together with beta adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta adrenergic blockers should be preferred, although they should be administered with caution. The co administration of Ultibro Breezhaler with other anticholinergic containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P glycoprotein (P gp), raises the systemic exposure of indacaterol up to two fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual components. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, musculoskeletal pain, dyspepsia, dental Caries, gastroenteritis, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest Pain, oropharyngeal pain including throat irritation, Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, bladder obstruction and urinary retention, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, pruritis/rash, paradoxical bronchospasm, epistaxis, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia, insomnia Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:** POM **PACK SIZES:** Single pack containing 6x1 or 30x1 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/001 - EU/1/13/862/003 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 4, Marsa, MRS 1000 Malta. Tel: +356 22983217/+35621222872 2014-MT-ULT-28-MAY-2014

References: 1. Novartis Europharm Ltd. Ultibro® Breezhaler® Summary of Product Characteristics. 2. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med. 2013;1:51-60. 3. Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 2013; 42(6): 1484-1494 doi: 10.1183/09031936.00200212. Epub 2013 May 30. 4. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199-209.

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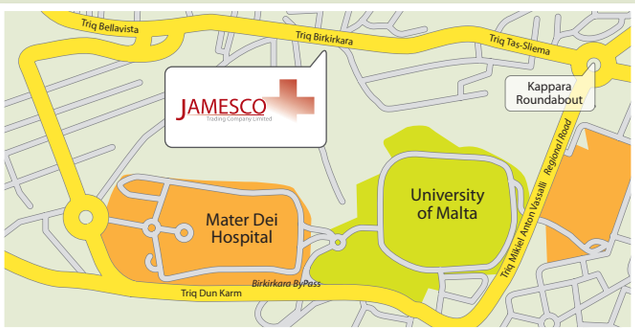

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ALBERT CILIA-VINCENTI

THE SLIPPERY SLOPE OF MODERN MEDICAL REPORTING – PART I

Doctors, let alone lay people, are bewildered by all the contradictory theories presented in current health books as result of the many studies being presented, usually for commercial purposes.

"Theory" in the medical field often means just a guess – frequently incorrect. In physics and engineering, say, "theory" means an accurate prediction of real-life results which will not be found to be incorrect a few years later. In contrast, the plethora of contradictory results of studies in medicine and nutrition often lead nowhere and are later reversed.

Most medical science isn't science at all. A true experiment is meaningful only when it can result in valid recommendations. These are rare in the medical field, because it is next to impossible to control a person's environment well enough to come to an accurate conclusion rendering many, if not most, studies of little worth.

If there are negative results in a study, then what was hoped to work is disproven. In mathematics, to prove a theorem is false, all you have to do is find one case where it is false – case closed. Why doesn't this happen in medicine? Simple – who is financing the studies? Nutritional and pharmaceutical companies often mislead doctors and lay people. To make accurate medical claims, a statistical analysis of the variable influences ("analysis of variance") must be done, and three conditions must be met to make statements that show cause and effect: (a) every factor must be taken into account that could influence the outcome (in advance), (b) the relative importance of each factor must be determined (in advance) and (c) the probable contribution of each factor to the result must be estimated (in advance).

The obvious problem is that unless you can keep someone in a cage for the duration of the study, it is virtually impossible to do the above. Furthermore, usually no one knows what other factors even need to be considered. "Negative" outcomes are therefore very important and studies claiming how well something works should not be taken at face value.

Dr Walter Willet of the department of nutrition at Harvard School of Public Health, interviewed by *Medscape Oncology* (April 22, 2009) discussed his presentation at the American Association for Cancer Research's 100th Annual Meeting, entitled, "Diet, Nutrition and Cancer: The Search for Truth".[1] In this overview, he reviewed many of the associations that had been suggested by epidemiological studies, including red meat, meat cooked at high temperature, a high fat diet and alcohol (claimed to increase the risk), and fruit and vegetables (claimed to decrease risk). He said, "much of the evidence for these links is rather weak", and "if there was a strong association, we would have seen it by now", and "even the case for vegetables and fruit is fairly weak when it comes to cancer".

Dr Marcia Angell, former editor-in-chief of The New England Journal of Medicine, says that most doctors are ill-equipped to critically assess the conclusions of researchers, adding, "it is very hard to find enough articles to publish. With a rejection rate of 90% for original research, we were hard pressed to find 10% that were worth publishing. So you end up publishing weak studies. She adds, "doctors are not sceptical enough about what they read in top journals".[2]

It is possible to design experiments that don't require "interpretation" of results or even statistics showing probabilities of outcomes being accurate. Biochemistry, physical chemistry, physiology, physics and engineering are all fields whose experiments rarely, if ever, are open to interpretation. Even in medicine and nutrition, there is much data that is invariably correct, where recognising a cause/effect relationship is mandatory or the field will not progress. For example, too much blood sugar always means diabetes – no need for interpretation.

The authors of a recent paper did in fact understand that a true cause/effect relationship requires demonstration of a positive effect on the subjects, otherwise it's thrown out as untrue. We had been led to believe that HDL cholesterol was anti-atherogenic, so the researchers expected to find a 13% decreased risk of myocardial infarction among those who were genetically predisposed to higher HDL levels. To their surprise, they found no association between a genetically predisposition to higher HDL levels and lower risk of heart attacks.[3] Clinical trials have failed to show that raising blood HDL reduces adverse cardiovascular events, but not all doctors are aware of this.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

A DOCTOR IN THE MAKING

MARIKA AZZOPARDI

There is no doubt that Jordan Camilleri is an athletic person. Even before discovering that he is a seasoned waterpolo player, his physique gives away his sport. This 22 year old medical student shares some of his experiences relating to sport and medicine in this short and candid interview.

Jordan's switch to waterpolo came as a natural progression. "We live just a few steps away from a waterpolo pitch in St Julian's and such a close proximity meant I was tempted to jump right in. But other factors contributed to this decision, namely that my older brother Stevie Camilleri is a professional waterpolo player and that, apart from all this, my father is a family doctor and also the Neptunes' waterpolo team doctor."

As a semi-professional waterpolo player, Jordan's training schedule can be pretty hectic. "I train throughout the entire year, with some three hours of training put in daily. We then get a roughly three-month summer period when, apart from training, we take part in the national championship. Besides playing with Neptunes, I am also on the National Waterpolo Team and have this year, already travelled twice with the team." In fact, the National Waterpolo Team, including Jordan, travelled to Limerick in Ireland for the 8-Nations Cup and won a gold medal in March. The team proceeded to land a silver medal in April during the Commonwealth Games held in Aberdeen, Scotland.

"The winter league serves mostly as a training preparation for the summer league which stretches from end May through to September. We play over 20 games every season, including games for the winning of domestic cups. For me, waterpolo is similar to a part-time occupation since I get paid for my playing which neatly adds on to my student's stipend. But in reality, waterpolo is so intrinsically inter-linked with my life, that I cannot for a minute, imagine living without the sport."

This sport does not stop him from his studies. If anything, he insists that physical exercise helps him unload his stress levels and concentrate better. "Many people think they should give everything up and just focus on study once they enter university. I am totally against this frame of mind. Free time is limited of course, and I am in a relationship which also needs time dedicated to it. But whilst many people think they would never manage to cope with a sport or any other hobby, they eventually regret having dropped things along the way. For myself, training serves as a valuable break during exams for instance, and I return to the books with better focus. I am by nature, a person who gets quickly irritated when stuck doing the same thing over and over, so the sport diversifies my energies. Then again, being part of a team teaches you a lot."

In several ways, he is used to being part of a team even at home, since he has grown up with three other siblings. "We get on very well together, myself, my brother and my two sisters, one older and one younger than myself. I am the third child. All my family backs my studies, especially my father since he has been through it himself. He makes sure all is in place to enable me to study and he supports me also by answering my million questions and sharing his knowledge with me. Yes, my studies in medicine have proved to be a great connection for us – I am very close to my father."

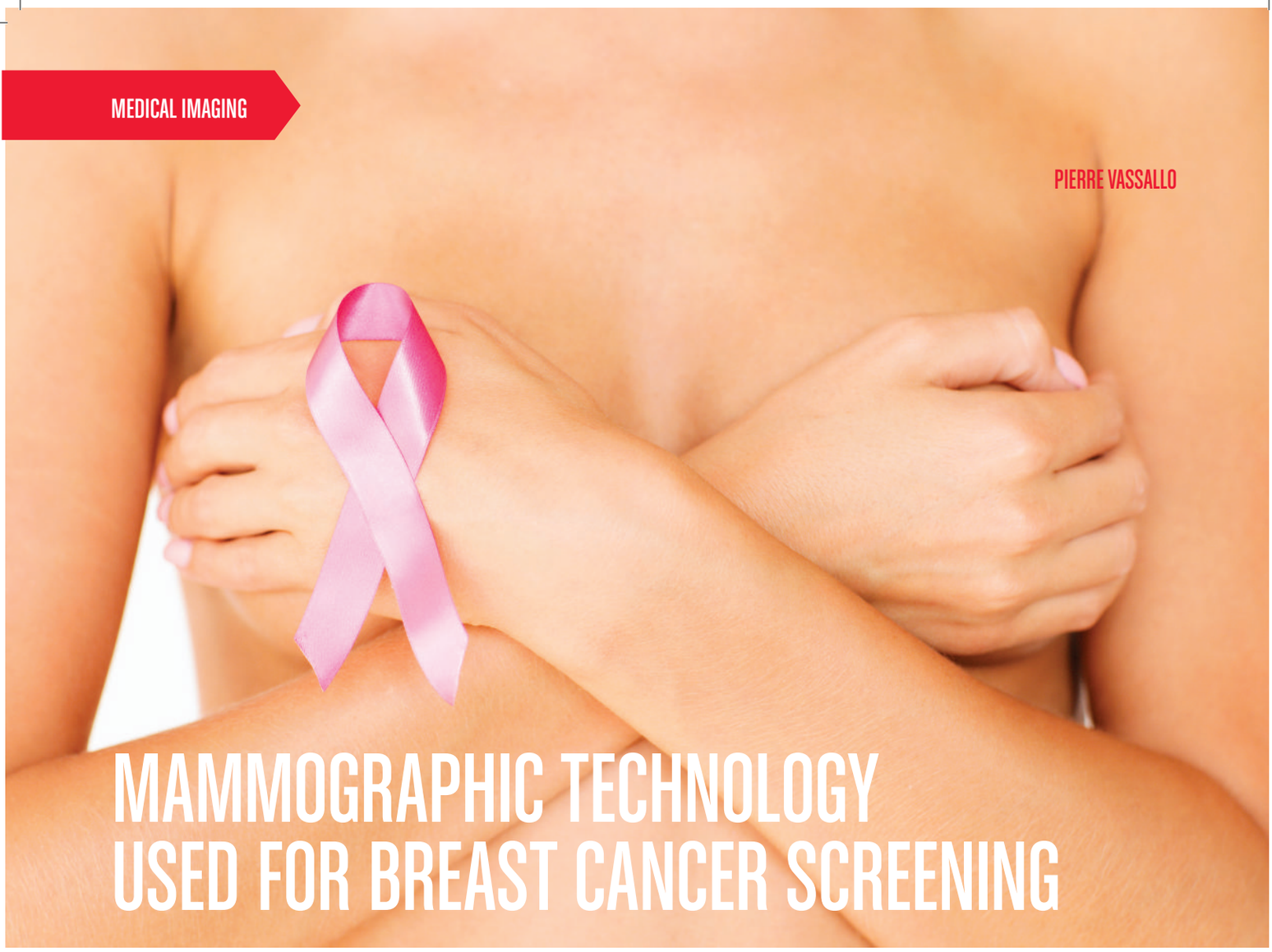
Asked about his experience at university so far, Jordan speaks about there being too much focus on books and not enough, in his opinion, on the clinical aspect of the training. "I understand it is difficult for a consultant to take along an unlimited number of students in tow for the ward rounds, but students crave for such experiences. For myself, I can say that this year's experiences in psychiatry, geriatrics and family medicine were invaluable and I especially learnt a great deal from my community attachment where I was assigned to a general practitioner at a health centre. The experience of being on a one-to-one basis with a practising doctor helped me learn a great deal."

'It-tifel tat-tabib' he may well be, but Jordan has in actual fact been strongly inspired by his father to take up medicine. It has helped that he was always brilliant at science topics in school. But living in a doctor's family has led him to appreciate the works behind the practice and it definitely has not put him off. "I have come to appreciate the profession. Although at this stage, I still don't know which aspect of medicine to delve into, I am just concentrating on graduating for now."

Neptunes WPSC team (Jordan is 4th from bottom right)

'IT-TIFEL TAT-TABIB' HE MAY WELL BE, BUT JORDAN HAS IN ACTUAL FACT BEEN STRONGLY INSPIRED BY HIS FATHER TO TAKE UP MEDICINE

PIERRE VASSALLO



MAMMOGRAPHIC TECHNOLOGY USED FOR BREAST CANCER SCREENING

Breast cancer, the most common cancer in women (1 in 8 women develops breast cancer), has generated considerable interest in the literature with the result that Breast Cancer Screening Programmes have become the norm in developed countries. The aim of these screening programs is to achieve early detection of breast cancer in women who have not yet developed any symptoms. Such early detection would allow early treatment, which is necessary to achieve a good treatment outcome. It has been shown that treatment of early cancer results in cure in 98% of cases, while late cancer detection results in a poor outcome.

Early breast cancer detection depends on the accuracy of the equipment used and on training and experience of the specialists involved. Equipment accuracy and consequently image quality play a very important role as specialist training and experience do not compensate for poor image quality. There is considerable scientific evidence confirming the advantages of digital mammography over conventional film-screen mammography.

Film-screen mammography uses a chemically processed film to record images of the breast. On the othr hand, there are two different technologies used in digital mammography, computed radiography (CR) or full-field digital mammography (FFDM).

CR is a technology that obtains an image of the breast through exposure of a fluorescent plate, which is then scanned in a dedicated laser scanner to obtain a digital image of the breast (Fig 1).

In contrast, FFDM technology uses an array of tiny solid-state electronic detectors embedded in the base plate of the mammography machine; the image of the breast obtained by these tiny detectors is transferred directly to a specialised computer workstation for viewing (Fig 2).

CR uses an intermediate step in processing, namely the fluorescent plate; this significantly degrades image quality. FFDM, a significantly more expensive technology, obtains images that are far superior to CR mammography (Fig 3).

FFDM has consistently been shown to be more accurate for detecting cancer than CR or conventional film-screen technology and is now considered the gold standard of mammography. In addition, FFDM uses 25-65% less radiation and is therefore much safer than other technologies.

FFDM breast cancer screening has a high detection rate for cancers particularly those containing calcifications (Fig 4a), most of which represent an early-stage cancer known as ductal carcinoma in situ (DCIS). Microcalcifications are defined as calcifications each measuring ≤0.5mm in diameter, and are particularly suspicious when >5 in number within an area ≤1cm in diameter, especially when distributed in a linear and branching (ductal) pattern and when they have a fragmented

FFDM USES 25-65% LESS RADIATION AND IS THEREFORE MUCH SAFER THAN OTHER TECHNOLOGIES

Figure 1a: CR mammography machine takes a cassette containing a fluorescent plate in the cassette holder (arrow).

Figure 1b. The CR laser reader withdraws the fluorescent plate from the cassette and scans it.

appearance. Microcalcifications may be very subtle (Figure 4b) and should raise clinical suspicion even at this stage. The visibility of microcalcifications is improved on FFDM compared with CR and film-screen mammography (Fig 5).

Invasive breast cancers, which are more advanced than DCIS, may also contain calcifications. In fact, around 35% of cancers detected on the basis of the presence calcifications are invasive breast cancers.

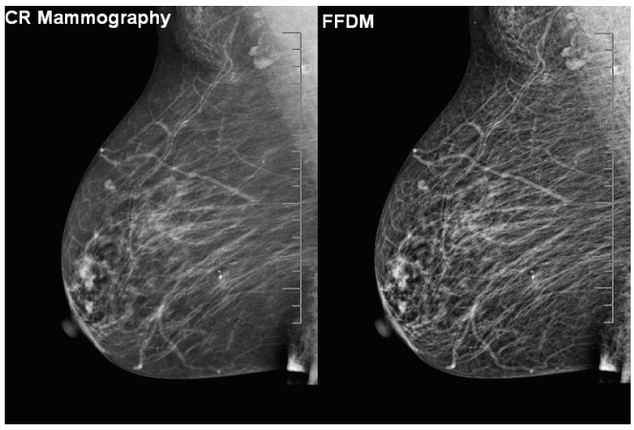
Invasive cancers detected on the basis of calcifications in population-based digital mammographic screening also tend to be smaller (median, 7 mm) than those detected on the basis of mass (median, 14mm), architectural distortion (median, 15mm), or combinations of both features (median, 17mm).

In addition, invasive cancers detected through the presence of calcifications noted on FFDM share the same degree of aggressiveness as those detected on CR and film-screen mammography; in other words, we are not detecting less aggressive and maybe less significant cancers with FFDM. Nevertheless, the calcification-based detection rate for invasive cancers in population-based screening is higher with FFDM than with CR or film-screen mammography.

Figure 2: FFDM machine contains an array of micro detectors in the base plate (arrow).

THE CALCIFICATION-BASED DETECTION RATE FOR INVASIVE CANCERS IN POPULATION-BASED SCREENING IS HIGHER WITH FFDM THAN WITH CR OR FILM-SCREEN MAMMOGRAPHY

Figure 3: Comparison of CR versus FFDM: noted the sharper and more detailed image obtained by FFDM compared to CR.



The improved image quality of FFDM does not contribute only to detection of breast calcifications. Subtle areas of architectural distortion are also better seen and are often the only sign of early malignant disease (Fig 6).

In summary, mammography is a valuable tool in the detection of early breast cancer and is our primary modality in breast cancer screening. The accuracy of mammographic technology however, varies depending on the method used. FFDM performs significantly better and has become the gold standard for use in breast cancer screening. CR and film-screen mammography although still widely available and in common use, should be replaced by FFDM as these technologies no longer meet the standards expected in today's clinical practice.

Figure 4a. Obvious microcalcifications distributed in a linear and branching pattern (arrows).

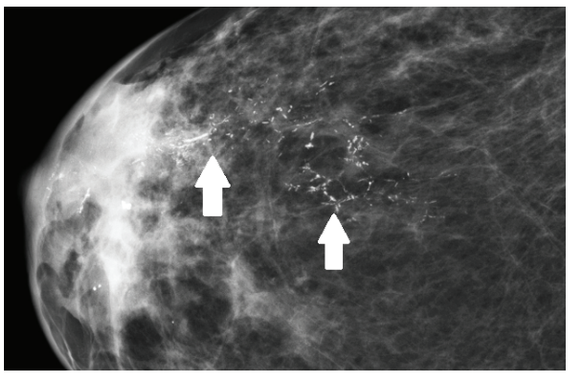


Figure 4b. More subtle fragmented microcalcifications in early DCIS (circles).

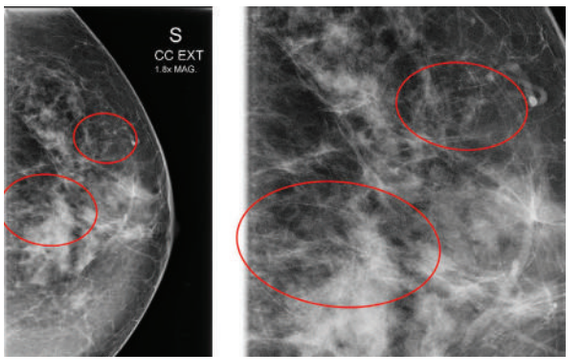


Figure 5: Comparison of microcalcifications seen on CR versus FFDM.

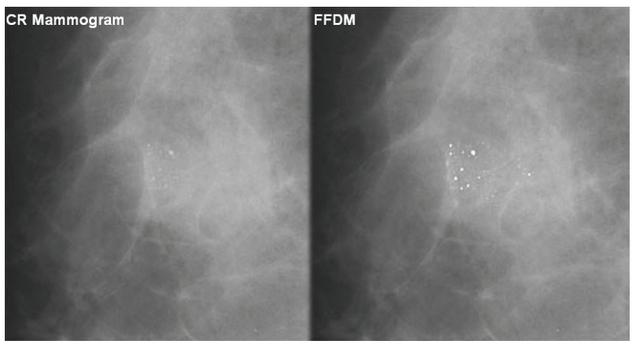
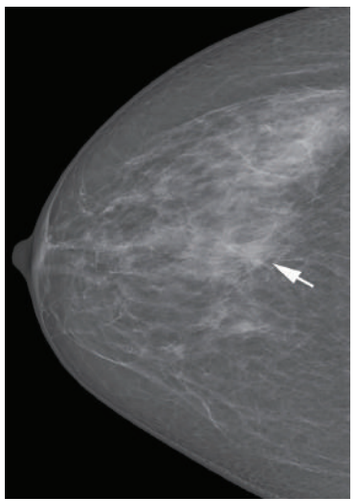


Figure 6. Very subtle early invasive ductal cancer detected through minimal architectural distortion (arrow) on FFDM. This would likely have been missed on film-screen or CR mammography.



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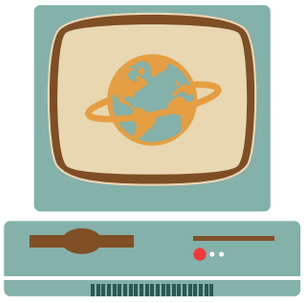

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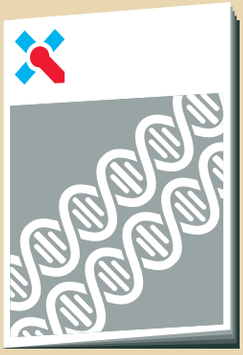

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2014 VIDEO

To coincide with the 18th anniversary of the launch of TheSynapse, and to complement its already very wide range of services offered to users, TheSynapse has recently reached another milestone by launching TheSynapse Video Section, bringing you local experts directly to your desktop or mobile device.

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We are very grateful to the speakers, all respected and eminent experts in their respective fields who accepted to participate in these programmes. We are sure that this series will rapidly grow to be a significant source of eLearning and continuing medical education to medical professionals in Malta and abroad.

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Prepared: October 2014
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