THESYNAPSE

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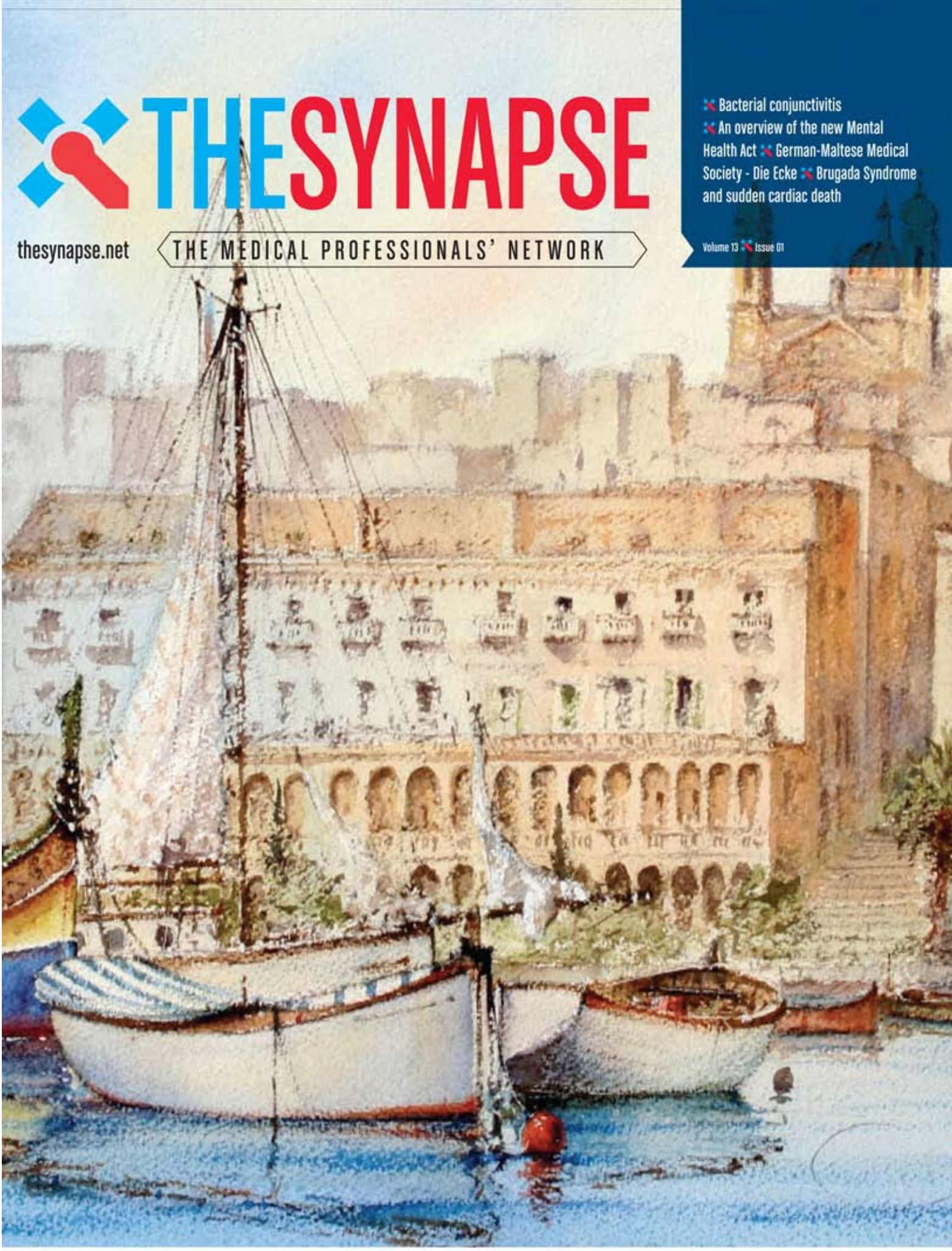
THE MEDICAL PROFESSIONALS' NETWORK

- Bacterial conjunctivitis
- An overview of the new Mental Health Act
- German-Maltese Medical Society - Die Ecke
- Brugada Syndrome and sudden cardiac death

Volume 13 Issue 01



GALVUS and EUCREAS

COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

GALVUS is a DPP-4 inhibitor that improves glycemic control through powerful islet enhancement[1]

EUCREAS is the combination of a DPP-4 inhibitor, GALVUS, and metformin[2]

Galvus® (vildagliptin) tablets

PRESENTATION: Each tablet contains 50 mg of vildagliptin **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults: As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with: metformin in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin; a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance; a thiazolidinedione in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. As triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy in combination with thiazolidinedione, in combination withmetformin and asulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Galvus in children and adolescents (< 18 years) have not been established. No data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients (≥ 65 years. The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis. Therefore Galvus should be used with caution in these patients . Galvus is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding since no studies on the effect on human fertility have been conducted for Galvus. Should be used with caution in patients with renal impairment. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). Monotherapy: Common (>1/100 to <1/10): dizziness. Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Combination with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia, hyperhidrosis, asthenia. Uncommon: fatigue. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharyngitis. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Uncommon: headache, asthenia, hypoglycaemia. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Uncommon: Diarrhoea. RebulenceFrequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions. **LEGAL CATEGORY:** POM **PACK SIZES:** 7, 28 tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/001, 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 / +356 21222872. 2013-MT- GAL-07-AUG-2013

Eucreas® (vildagliptin/metformin hydrochloride) film-coated tablets

PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. **DOSAGE:** The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. *Vildagliptin Monotherapy:* Common (>1/100 to <1/10): dizziness. Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. *Metformin monotherapy:* Very common (>1/10): Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. *Combination vildagliptin with metformin:* Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. *Combination with metformin and sulphonylurea:* Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. *Combination with insulin:* Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence. For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:**POM **PACK SIZES:** 30, 60 film-coated tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/002–003, EU/1/07/425/008-009. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta Tel +356 22953217 / +356 21222872 2013-MT-EUC-31-JUL-2013

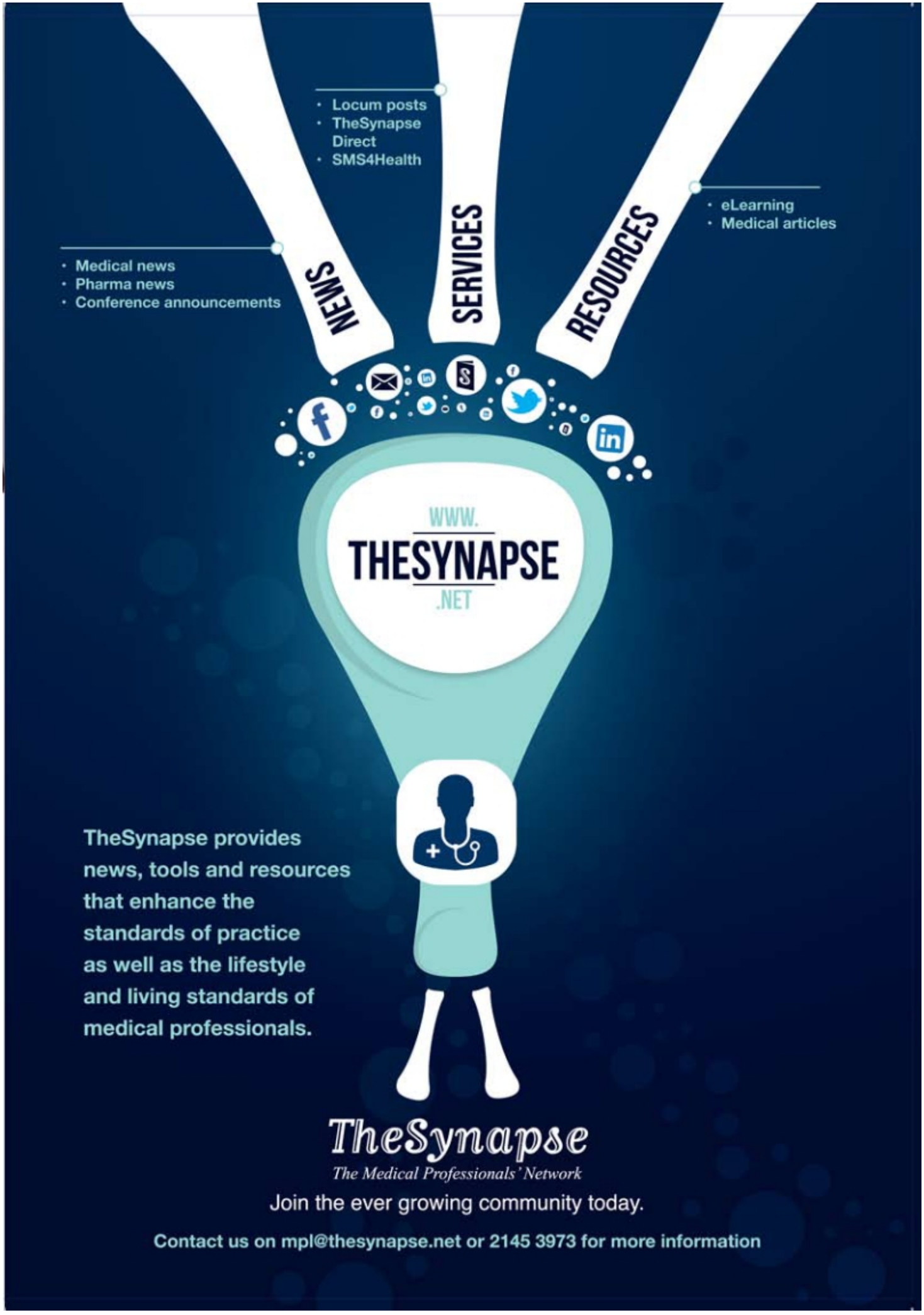
GAL Ad1 01/14 MT

NOVARTIS PHARMACEUTICALS

1. Novartis Europharm Ltd. Galvus® Summary of Product Characteristics
2. Novartis Europharm Ltd. Eucreas® Summary of Product Characteristics

Galvus vildagliptin

Eucreas vildagliptin/metformin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PHARMA'S KRYPTONITE

2014 will herald existing and new challenges for the pharmaceutical industry. Diminishing pipelines, increasing development costs, generic competition … pharmaceutical companies are under constant pressure to innovate and collaborate if they want to survive. As a point of fact, over 700 biotechnology and pharma takeovers have occurred in the past four years.

Although recent years have seen increases in R&D investment, yet new drug launches are fewer and far between. The age of the blockbuster drug is foregone, with many drugs coming off-patent. Furthermore, advances in human genome mapping are increasing the demand for personalized medicines.

In my opinion, two strategies should be embraced more thoroughly by the pharmaceutical industry.

1. INCREASE PERSONALISATION OF DRUGS

In the US, PricewaterhouseCoopers expects the annual market for personalised medicine to grow by 11% and be worth $452 billion by 2015. Identifying the patient populations for which a drug will be most effective is a win-win situation. Patients' lives will be improved, the governments will save money by only giving treatments that work, and the pharmaceutical industry can benefit from value-based pricing structures.

2. QUICKLY UNDERSTAND AND MAXIMISE THE VALUE OF ORPHAN DRUGS

This can be shown by the following example. Botox® started out life as Oculinum®, an orphan drug for uncontrolled blinking, neck pain and muscle spasms. Once the drug was being used, physicians reported unexpected adverse events including a more youthful appearance and the relief of migraines. While sales of the drug top $1.5 billion a year in the US alone, it took almost 20 years for the company to get FDA approval for the treatment of frown lines. It took a further eight years for it to gain approval for the treatment of migraines. Presumably, if the marketing authorisation holder of Botox® had been able to tap into available data about Oculinum®, it could have identified its more lucrative uses – and the demand – much more easily and quickly.

Against this backdrop of a search for a holy grail, I seek refuge in popular fiction. Maybe the answer lies in devising bed-sized medical devices similar to those shown in *Elysium* [*Med-Bays*] which can cure people from all ailments, ranging from missing limbs to all types of cancers, thru' a re-atomizing process. Or maybe the answer simply lies in the album ***Fitness to Practice*** which was produced in 2004 for charity by medics Dr Adam Kay and Dr Suman Biswas. *Paracetamoxyfrusebendroneomycin* is a [fictitional] medicine produced from the cerebellar cortex of a bison, and can be used to treat "anything from leprosy to SARS"; it thus enables medical students to avoid the study of pharmacology! Unfortunately, despite being a universal panacea, this whooping 31 letter innovation has some serious adverse reactions with the writers quoting "heart attacks, becoming gay, and growing extra breasts" as an example … but I am sure that with today's knowledge these challenges can be overcome!

Ian Ellul

Cover:
Boats in front of Dar Sant Anna - Senglea
by John Martin Borg

Editor-in-Chief: Wilfred Galea
Managing Editor: Ian C Ellul
Sales & circulation director: Carmen Cachia

Email: mpl@thesynapse.net
Telephone: +356 21453973/4

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OUR COLLABORATORS

Have you asked your patients with COPD about their mornings?

MANY PATIENTS FEEL COPD SUCKS THE BREATH OUT OF THEIR MORNINGS.[1,2]

› Seebri® Breezhaler® is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

Model is for illustrative purposes only.

NEW

INTRODUCING ONCE-DAILY SEEBRI BREEZHALER®

A NEW INHALED ANTICHOLINERGIC FOR PATIENTS WITH COPD.[3]

SUCCINCT STATEMENT SEEBRI® BREEZHALER®

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 immediately 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

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 124, Valletta, VLT 1000, Malta. Tel: +356 22983217/21222872

2013-MT-SBR-14-AUG-2013

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

References: 1. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey [published correction appears in Curr Med Res Opin. 2012;28(8):1405]. Curr Med Res Opin. 2009;25(8):2043-2048. 2. Barnett M. Chronic obstructive pulmonary disease: a phenomenological study of patients' experiences. J Clin Nurs. 2005;14(7):805-812. 3. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J. 2011;37(2):264-272. 4. Novartis Europharm Ltd, Seebri® Breezhaler® Summary of Product Characteristics.

Please see SPC for full prescribing information.

NOVARTIS

Once Daily seebri® breezhaler®
glycopyrronium bromide inhalation powder

SEE Ad1 01/14 MT

AUTHORS

Dr Nigel Camilleri
MD MRCPsych, CCT(Child and adolescent psychiatry)
is a consultant psychiatrist in Durham, UK, and an associate clinical researcher at Newcastle university reading for a post graduate MD in young people with complex mental disorders.

Dr Anthony Zahra MD MRCPsych (UK) MSc GER (Soton)
is a specialist in Psychiatry, graduating from the UOM in 2004, followed by a MRCPsych in 2010 and a postgraduate degree in Gerontology from the University of Southampton in 2011. He currently works as a specialist in acute, general adult, community and old age psychiatry, and also lectures at the UOM. He may be contacted on anthony.zahra@gmail.com

Dr Melvin J. Gouder MD MRCOphth(UK) MRCSEd(Ophth)
is a consultant ophthalmic surgeon with special interest in Cataract and Vitreo-Retinal surgery. He trained in England and Scotland and currently practices at Mater Dei Hospital and Saint James Hospital. He has an interest in LASEK refractive surgery and also carries out simple and complex paediatric and adult strabismus surgery.

Alexander Grima
is a fourth year medical student at the UOM. He has a keen interest in student activism having occupied numerous posts in the MMSA and attended a number of both student and academic conferences.

Dr Nikolai P Pace MD PhD
is a lecturer and researcher at the Faculty of Medicine and Surgery, UOM. His research focuses on the genomics of type 2 diabetes and obesity.

Dr Pierre Vassallo MD PhD FACA Artz fur Radiologie
specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Hospital, Malta.

Dr Samuel Meilak MD
is a second-year Foundation Doctor at Mater Dei Hospital who has cardiology at heart. He is also a casual lecturer within the Faculty of Medicine and Surgery at the UOM. The co-author of the article is Dr Mark Sammut.

ISSUE GUIDE

TheSynapse

FOCUS ON

BACTERIAL CONJUNCTIVITIS

MELVIN J. GOUDER

INTRODUCTION

Bacterial conjunctivitis is a very common ophthalmic condition that can affect anyone from day one of life to old age[1]. It is one of the commonest reasons for self-referrals of patients visiting eye specialists. It is defined as an inflammation of the conjunctiva by bacteria where the palpebral, bulbar and forniceal parts of the conjunctiva become hyperaemic. The infection can be acute, hyperacute or chronic. Contrary to popular belief it can be self-limiting but it is frequently treated with broad-spectrum antibiotics most commonly in drop form[2]. Very rarely it can progress to complications such as keratitis (corneal infection) or pre-septal cellulitis (skin infection of the lids)[3].

CAUSATION

There is a whole host of pathogenic bacteria that can cause this kind of benign ocular pathology[4]. The spectrum of bacteria includes *Neisseria, Staphylococcus Haemphilus, Moraxella* and Chlamydia species, as well as thehighly virulent form of *Streptococcus pneumoniae*. The acute form is commonly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* or one of the *Haemophilus* species. *Moraxella* and *Chlamydia* can cause a chronic form. Clinically, *Chlamydia* can cause a non-purulent form of conjunctivitis with symptoms more synonymous of a viral infection like adenoviral conjunctivitis.

RISKS

The most common risk factor to acquire all forms of bacterial conjunctivitis is coming in contact with an infected individual[5]. However other risks include poor drainage of tears such as in nasolacrimal duct obstruction (NLDO), lid malposition such as entropion or ectropion (also interfering with lacrimal drainage), severe tear deficiency as in Sjogren syndrome and the associated autoimmune diseases. These conditions hinder the natural resistance mechanisms of the eyes. Patients on immunosuppressive agents such as steroids are at greater risk, as are older fragile patients. Good hand hygiene and limiting direct contact with infected individuals reduce the risks.

SYMPTOMATOLOGY AND SIGNS OF BACTERIAL CONJUNCTIVITIS

The differential diagnosis of bacterial conjunctivitis includes its viral form, the allergic variant and less commonly, conjunctivitis secondary to chemical exposure. All the signs and symptoms can be similar but in bacterial conjunctivitis there are some specific features. A purulent discharge that can have mucoid characteristics, irritation, diffuse conjunctival hyperaemia and bulbar conjunctival injection are all features that occur first in one eye but then commonly spread to the fellow eye.

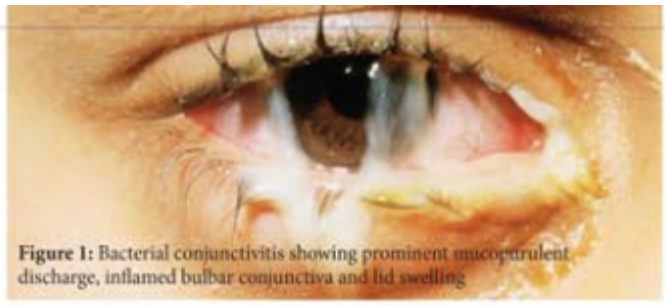

Figure 1: Bacterial conjunctivitis showing prominent mucopurulent discharge, inflamed bulbar conjunctiva and lid swelling

DIAGNOSIS

The diagnosis is most commonly clinical[1]. The patients' description that they might have come in contact with an infected individual also helps diagnosis. Full ophthalmic examination is necessary, including slit-lamp biomicroscopy to exclude intraocular pathology. If there is an associated keratitis one might observe a secondary reaction in the anterior chamber which may warrant treatment. Additional diagnostic tests are usually reserved for recurrent and/or chronic cases which are unresponsive to the initial medication. These include cultures, stains, smears and immunoassays. Typically in a chronic conjunctivitis one might need to specifically screen for viral causes (*Herpes*) and *Chlamydia* apart from cultures for the other forms of stubborn bacteria.

TREATMENT

The gold-standard treatment is with a broad-spectrum antibiotic in drop or ointment form for 5-7 days and is commonly effective. As mentioned above, it can also be self-limiting but treatment may reduce the symptoms and duration of the disease. Recurrence rates are lower in treated cases.

Sometimes aminoglycosides are not considered to be broad-spectrum antibiotics due to their poor activity against *Streptococci*[6]. Chloramphenicol resistance has become very common so it is not popular amongst ophthalmic surgeons[5]. On the other hand, erythromycin ointment is not commonly prescribed but is usually reserved for Chlamydial infections. It was traditionally a hospital item.

Fluoroquinolones are in their 4th generation (moxifloxacin) and Can also be used in patients with infection related to contact lens misuse such as keratitis.

CONCLUSION

Though benign, bacterial conjunctivitis should never be treated lightly especially in older patients who are to undergo cataract surgery. Any suspicion of infection in these patients should be initially treated with topical antibiotics. One should wait clearance from sensitivity tests to ensure that the eye is free from pathogenic bacteria that can potentially cause acute post-operative bacterial endophthalmitis. There are ophthalmic surgeons who prefer to treat high-risk patients (diabetics and the immunocompromised) with a pre-operative course of 4 days with a 4th generation fluorinated quinolone like moxifloxacin.

Table 1: *Commonly* used antibiotics in bacterial conjunctivitis in Malta

Antibiotic group	Example	Mode of Action
Aminoglycosides	Gentamicin Tobramycin	Protein synthesis inhibition
Chloramphenicol	Chloramphenicol	Protein synthesis inhibition
Fluoroquinolones	Ciprofloxacin Moxifloxacin	Interferes with DNA synthesis

When it comes to pink eye we don't play around.

Vigamox®

(moxifloxacin 5 mg/ml eye drops solution)

Count on the proven efficacy of moxifloxacin

In a multicenter comparative clinical trial in which patients with bacterial conjunctivitis were dosed 3 times a day for 7 days[1*]

81% of patients achieved complete resolution of ocular signs and symptoms after 48 hours[1*]

Patients should be instructed to follow the full 7-day course of therapy.

NAME OF THE MEDICINAL PRODUCT: VIGAMOX 5 mg/ml eye drops, solution. **Therapeutic indications:** Topical treatment of purulent bacterial conjunctivitis, caused by moxifloxacin susceptible strains. Consideration should be given to official guidance on the appropriate use of antibacterial agents. **Posology and method of administration.** Ocular use: Use in adults including the elderly The dose is one drop in the affected eye(s) 3 times a day. The infection normally improves within 5 days and treatment should then be continued for a further 2-3 days. If no improvement is observed within 5 days of initiating therapy, the diagnosis and/or treatment should be reconsidered. The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course of infection Paediatric patients No dosage adjustment is necessary Use in hepatic and renal impairment No dosage adjustment is necessary **Contraindications** Hypersensitivity to the active substance, to any of the excipients, or to other quinolones. **Special warnings and precautions for use:** In patients receiving systemically administered quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial oedema), airway obstruction, dyspnoea, urticaria, and itching. If an allergic reaction to VIGAMOX occurs, discontinue use of the medicinal product. Serious acute hypersensitivity reactions to moxifloxacin or any other product ingredient may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated. Data are very limited to establish efficacy and safety of VIGAMOX in the treatment of conjunctivitis in neonates. Therefore use of this medicinal product to treat conjunctivitis in neonates is not recommended VIGAMOX should not be used for the prophylaxis or empiric treatment of gonococcal conjunctivitis, including gonococcal ophthalmia neonatorum, because of the prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae*. Patients with eye infections caused by *Neisseria gonorrhoeae* should receive appropriate systemic treatment. The medicinal product is not recommended for the treatment of *Chlamydia trachomatis* in patients less than 2 years of age as it has not been evaluated in such patients. Patients older than 2 years of age with eye infections caused by *Chlamydia trachomatis* should receive appropriate systemic treatment. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition, e.g. systemic treatment in cases caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. Patients should be advised not to wear contact lenses if they have signs and symptoms of a bacterial ocular infection. **Interaction with other medicinal products and other forms of interaction** No specific interaction studies have been performed with VIGAMOX 5 mg/ml Eye Drops, Solution. Given the low systemic concentration of moxifloxacin following topical ocular administration of the medicinal product (see Section 5.2), drug interactions are unlikely to occur. **Pregnancy and lactation** Pregnancy There are no adequate data from the use of VIGAMOX in pregnant women. However, no effects on pregnancy are anticipated since the systemic exposure to moxifloxacin is negligible. The medicinal product can be used during pregnancy. Lactation It is unknown whether moxifloxacin is excreted in human breast milk. Animal studies have shown excretion of low levels in breast milk after oral administration of moxifloxacin. However, at therapeutic doses of VIGAMOX no effects on the suckling child are anticipated. The medicinal product can be used during breast-feeding **Effects on the ability to drive and use machines** As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient should wait until their vision clears before driving or using machinery **Undesirable effects:** Blood and lymphatic system disorders Uncommon: haemoglobin decreased, Nervous system disorders Common: dysgeusia, Uncommon: headache, paraesthesia Eye disorders Common: eye pain, eye irritation, dry eye, eye pruritus, conjunctival hyperaemia, ocular hyperaemia Uncommon: corneal epithelium defect, punctate keratitis, corneal staining, conjunctival haemorrhage, conjunctivitis, eye swelling, ocular discomfort, vision blurred, visual acuity reduced, eyelid disorder, erythaema of eyelid, abnormal sensation in eye Respiratory, thoracic, and mediastinal disorders Uncommon: nasal discomfort, pharyngolaryngeal, sensation of foreign body (throat) Gastrointestinal disorders Uncommon: vomiting Hepatobiliary disorders Uncommon: alanine aminotransferase increased, gamma-glutamyltransferase increased Paediatric population Based on data from clinical trials involving paediatric patients, including neonates (see section 5.1), the type and severity of adverse reactions in the paediatric population are similar to those in adults **Overdose** No case of overdose with VIGAMOX has been reported. The limited holding capacity of the conjunctival sac for ophthalmic products practically precludes any overdosing of the medicinal product. **Shelf life** 3 years Discard 4 weeks after first opening. **MARKETING AUTHORISATION HOLDER SA** Alcon Couvreur NV Rijksweg 14 B-2870 Puurs Belgium **MARKETING AUTHORISATION NUMBER:** MA015/01301. PLEASE VIEW FULL SmPC FOR COMPLETE DETAILS

References: 1. J Pediatr Ophthalmol Strabismus. 2008 Nov-Dec;45(6):340-9. 2. Data on file. Alcon Laboratories, Inc.

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AN OVERVIEW OF THE NEW MENTAL HEALTH ACT FOR THE MALTESE ISLANDS

ANTHONY ZAHRA & NIGEL CAMILLERI

Legal notice 276, published in September 2013, has set out the time windows for the implementation of the Mental Health Act, which was approved by parliament in 2012. The changes are expected to be rolled out over a period of one year, with the totality of the Act being in force by 10th October 2014. The first set of changes, implemented last November, brings in effect the first half of the provisions of the Mental Health Act.

Overall the proposed Mental Health Act is much improved on the previous Act; it reads well and brings the law up to date with modern psychiatry practice. At first glance the Maltese Mental Health Act seems to stem from the basis of the UK 1983 Mental Health Act as amended in 2007, although the authors are not familiar with other EU Mental Health Acts, therefore they could not comment on whether there are resemblances to other Acts.

IN THE SECTION BELOW, THE AUTHORS WILL DISCUSS AND MAKE COMMENTS ON SOME OF THE SEMINAL PARTS OF THE NEW MENTAL HEALTH ACT

Article 2 defines the many terms used in the Act. Of particular note is the term *mental disorder,* which has been pegged to disturbances of thought, mood, volition, perception, cognition, orientation or memory, to a degree that would be considered as pathological in international classifications. This is particularly useful in that it sets widely recognisable evidence-based standards, which are in turn supported by extensive field trials. However the authors point out in the definition of mental disorder, "*...considered pathological in accordance with internationally accepted medical and diagnostic standards....*" We believe that this leaves a definition which may be too broad in the determination of classificatory systems to be used. This may result in the possible idiosyncratic use of different diagnostic systems which have varying input of field tests and evidence-base. A specific reference to the International Classification of Diseases (WHO) or the Diagnostic and Statistical Manual of mental disorders (APA) may provide more definite guidance to the users of the Act as to which classificatory systems to refer to.

Part IV 7(2)(e): 'shall have a multidisciplinary care plan formulated in consultation with the patient and, or the responsible carer and finalised within 168 hours of admission.' One of the authors questioned what will the patient do and receive in the terms of care package in those seven days during admission to hospital? The authors are aware that the formulation of a care plan takes time to process, however a best practice suggestion could be that an initial care plan should be written up in the first 48 hours of the patients' admission into hospital, after which such care plan would be elaborated in more depth to meet all the needs of the in-patient over the following 5 days. As a result, the patient's management would commence as soon as possible, thus potentially reducing the acute impact of the condition and enabling his/her stay to be a short as possible. The outcome would be of benefit to both the in-patient and the service, as this will result in higher turnover rates of patients and lower mean number of days in hospital stays.

It is best clinical practice that a care plan and a discharge plan are formally drawn up in the immediate early phases of admission, whilst the law prescribes the maximum amount of time allowed for the formulation of such a plan. It should not be taken to mean that the law is prescribing the minimum number of days stipulated to write up a care plan, but the maximum. Further to this, the clinical focus of the clinicians remains upon devising a care plan formulation at the earliest, in the best interest of the in-patient, whilst being mindful of the legal parameters.

Part IV 7(3): This is a proviso which allows "in cases of voluntary admissions the nurse in charge of the patient may prevent self discharge for up to four hours to allow review by a medical practitioner if it is perceived that there are grounds for involuntary admission." This seems to be based on section 5.4 of the UK Mental Health Act. The Act specifies "*the nurse in charge of patient*"; does that mean there will be a named key worker/care coordinator who will be responsible for the care of each patient (based on the Choice and Partnership Approach (CAPA)) model in the UK? If this is the case, if the appointed nurse is not on duty, then who becomes the nurse in charge? And what does 'nurse in charge' actually mean? In the UK, this falls within the remit of responsibilities of a registered mental health nurse. Shifted to the local context, would this be a nurse specifically trained in mental health or any nurse working on

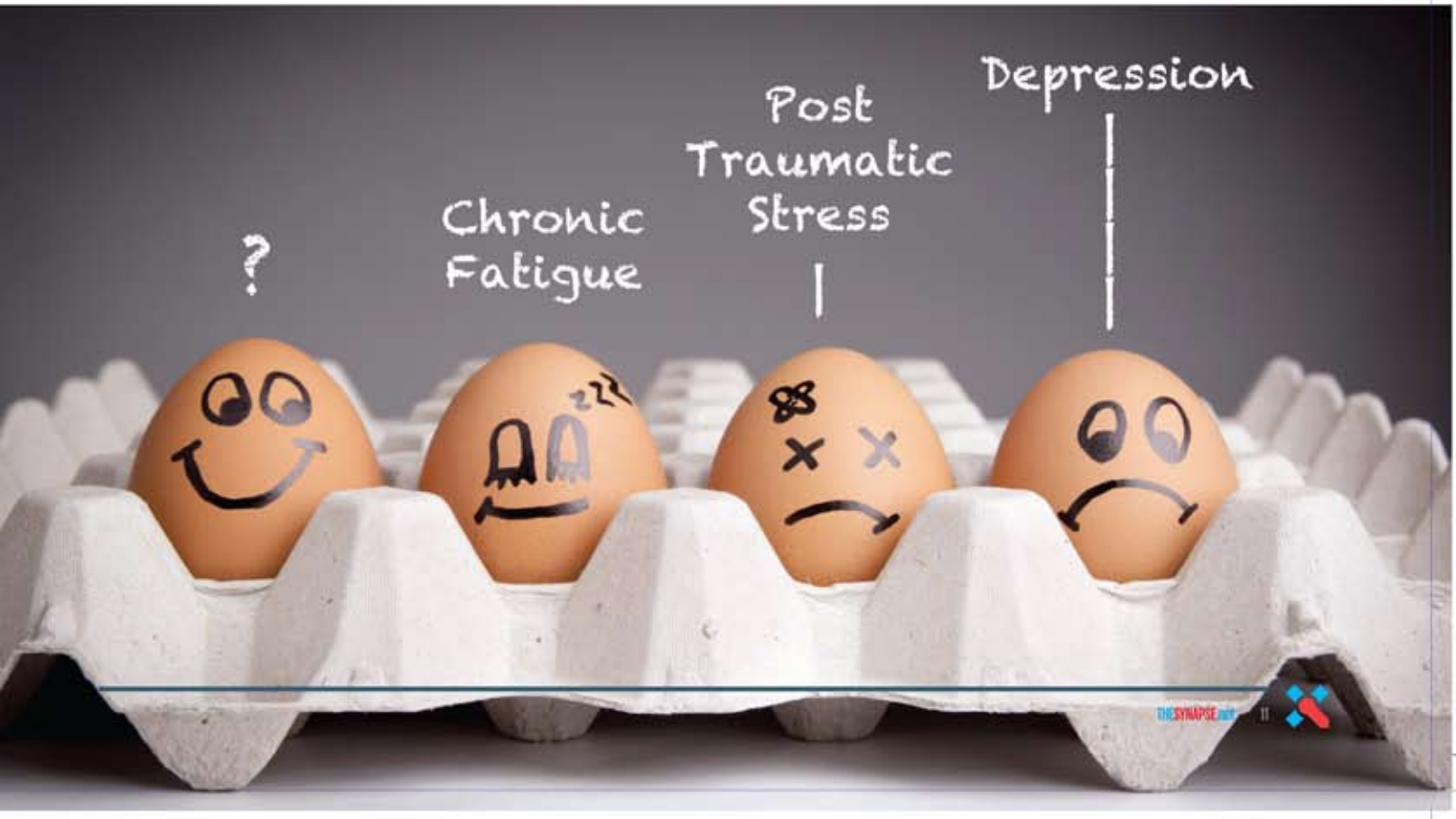
the ward who happens to be duty on the day? The authors feel that an action to detain a voluntary patient is a serious decision requiring formal mental health training, so limiting this responsibility to nurses who are specifically trained in the field would improve the standard of care.

Part IV 9(1). 'Prior to an involuntary admission for observation, an initial medical assessment shall be made by two medical practitioners, one of whom shall be a specialist'. Within the framework of the new Act, two doctors, one of whom being a specialist in mental health, need to provide a recommendation within 72 hours of each other. The application has to be signed by a responsible carer who is appointed by the patient, and in the absence of such, an approved mental welfare officer may apply for admission. In the case of disagreement between the two doctors responsible for the recommendation process, a third independent person, being also a specialist in psychiatry, will carry out an assessment, with the majority recommendation prevailing. This process promotes greater autonomy, in that the responsible carer nominated by the patient will be ultimately responsible for the application process. It is worth noting that provisions exist within the law for the substitution of carers through the Commissioner of mental health if there is reasonable doubt that the carer may not be acting in the patient's best interests.

In the UK it is the approved mental welfare officer (AMPH) who is responsible for organising the admission process. The AMPH is one of the three people needed to be present to organise and carry out the assessment to decide on whether or not the patient should be detained involuntarily. It is considered good practice for the three professionals to carry out the assessment together; this will result in asking a similar set of questions once and providing room for discussion following the same patient review. That way you get a medical perspective but also a social care perspective, which is also useful as there is a multidisciplinary approach adopted from the start. This system also helps to solve any problem which arise when you have two people who don't agree on an outcome; in this case, with three persons, there will always be a majority agreement. The two doctors have a responsibility to make a recommendation after which the AMPH takes a final decision.

Part IV 9(2): The presence of the emergency order has its advantages, especially when there is a lack of specialists who can assess potential admissions in the community prior to admission. In Malta, the emergency order is made use of frequently when it comes to admit a patient into a mental health hospital. This has been a loophole which has been used by many doctors, who refer patients for involuntary admission to a psychiatric hospital, however, as a result, this leaves the psychiatrists at of the acute inpatient admission phase without any power to take an expert decision on whether or not the person needs to be admitted or not. The authors believe that basing the admission decision solely on one medical recommendation leaves room for potential misuse. As a matter of practice, there should be a best practice clinical direction making an emphasis that the observation order is to be used as first priority. That is the reason why an observation order gives both parties 72 hours to fill in both forms; from a practical side, two doctors, one of whom being a specialist in mental health, should be possible to find.

Part IV 10(2): The current role of responsible relative has been expanded to that of a *responsible carer*, and extends beyond marital and familial relationships to include persons of trust that are nominated by the patient. This allows a greater degree of autonomy. Whilst at prima facie it would appear that the trusted person will act in the patient's best interest, this clause leaves a lot of power in the hands of the trusted person which may not reflect the patient's intentions. After all, this is a decision about mental health, which is a medical disorder based on



international diagnostic criteria, making it an objective decision. There is a complex issue of competence for a person with an acute mental disorder with lack of insight to choose a person of trust at that moment in time. Would this person of 'trust' be chosen beforehand using an advance directive? The authors agree that the nearest relative should be consulted for a collateral history and involved fully in the decision making process and care planning; however the application process may be safer if an approved mental welfare officer is involved.

Part IV 11(1): Whilst the observation order is valid for 10 days, there seems to be no clause on whether or not medication could be given during this time, unless in urgent situations and to prevent further deterioration. This period may not be sufficient to ensure the treatment of a mental disorder. It will be useful to audit the number of patients who will be converted to a treatment order and determine any correlation with the newly implemented decreased length of time of the observation order.

Part IV 16: The community treatment order seems to be based on the UK Mental Health Act; it reads well and is practical.

Part V 24(2): The Act states: 'Only a specialist may certify a person suffering from a mental disorder as having mental capacity or lack thereof'.

The law determines that the specialist needs to be a mental health specialist. All doctors should be trained in assessing capacity since a patient's health is the responsibility of any doctor; the doctor should be empowered to carry out an assessment of capacity in the first instance. However, if a second opinion is needed, then a psychiatrist is involved on a case by case basis. It is however noteworthy that within this Mental Health Act, capacity of understanding is mostly restricted for the management of civil matters, and issues of capacity falling within the remit of the mental health act need to be assessed by a specialist in mental health. It is necessary that further legislation is developed to fully regulate all aspects of the capacity and competence, including medical decision making.

The many other changes to be introduced in 2014, including the definition of the role of Commissioner for Mental Health, clear informed consent, services and treatment for underage persons, prescription of restrictive care, prisoners with mental health problems, the licensing of facilities for the provision of mental health care and commitment towards social inclusion will be addressed in later articles. Our impression is that the underlying drive and values in the 2012 Mental Health Act is to make the law more consonant with changes that have permeated the practice of mental health care, respecting autonomy, providing humane and expert care, whilst providing further checks and balances to ensure transparency and professional accountability.

WHAT ARE THE PRACTICAL IMPLICATIONS OF THIS MENTAL HEALTH ACT FOR PROFESSIONALS?

Many family doctors encounter the use of the Mental Health Act when faced with a situation where a person presents with an acute mental disorder which poses a threat to either the person or other parties. In circumstances where a period of containment and observation is warranted, even if such a measure is not acknowledged by the patient involved, the Mental Health Act specifies that an involuntary admission to a mental health setting may be invoked. Up to October 2014, there will be no changes in the period of time for which an emergency order will remain valid. The new projected timeframes will be introduced at that point.

In conclusion, furthermore to the above, the authors suggest that the best practice for professionals would be to utilise the *admission for observation* in all circumstance unless there is truly an emergency, by this we mean a physical lack of doctors present to assess and make a recommendation for involuntary admission over a 72 hour period. We believe it would be useful for the Commissioner of Mental Health and/or the Malta Association of Psychiatrists to set up educational lectures or issue best practice guidelines, to be used by all professionals, furthering one's understanding of which section of the Mental Health Act should be used in specific clinical scenarios. In cases of encountered difficulties, it would be a safe and feasible option to approach the office of the Commissioner for Mental Health to seek clarification.

WHAT HAS CHANGED IN OCTOBER 2013?

- Within mental health services, informed consent for any form of therapy shall be formalised through the use of a standardised form
- The use of restraint, including the use of single rooms, shall be limited solely to periods of acute behavioural dyscontrol
- The use of electro convulsive therapy shall need the approval of two specialists, even when the patients are able to provide informed conset
- Introduction of terms and statutory offices aimed at introducing more checks and balances at a clinical and administrative level

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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 where 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. pneumoniae. 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 exanthematous 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 authorisation 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. 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Reference: 1. H. Stoorgens et al. International Journal of Clinical Pharmacology and Therapeutics. 2004; 42: 165–173

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POLYCYSTIC OVARY SYNDROME

Polycystic ovarian syndrome (PCOS), previously referred to as Stein-Leventhal syndrome, is a worldwide disorder affecting about one fifth of women in their reproductive years[1]. It causes disturbances in reproductive, endocrine and metabolic functions. PCOS is the focus of a great deal of research and studies indicate that its prevalence is on the increase[2].

The main characteristics of PCOS are ovulatory dysfunction, hyperandrogenism, insulin resistance and obesity but one needs to investigate and exclude other functional disorders which may resemble PCOS. A key feature of the PCOS is an increased level of luteinizing hormone (LH) which may prevent the maturation of the ovum when it completes the first meiotic division and may thus be responsible for causing infertility in some women.

DIAGNOSIS

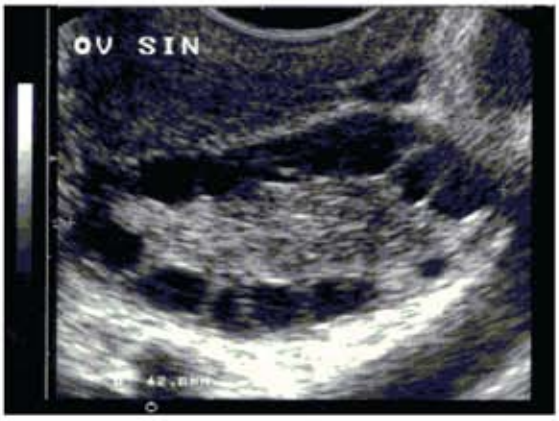
The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) state that in order for a woman to be diagnosed with PCOS, she must present with at least two criteria out of the following: 'oligomenorrhea and/or anovulation, hyperandrogenism (clinical and/or biochemical) and polycystic ovaries, with the exclusion of other etiologies'[3].

Azziz[4] states that the diagnosis of PCOS is essentially one of exclusion and that it can only be determined after ruling out thyroid dysfunction, androgen-secreting tumours and drug-induced hyperandrogenism.

The diagnosis consists of two principal steps:

1. **Identifying features which suggest that PCOS may be present, such as:**
   - long-term menstrual dysfunction or irregularity
   - hyperandrogenism, such as hirsutism, acne and alopecia
   - polycystic ovaries (Figure 1)

Figure 1: Ultrasound scan showing polycystic ovaries (herkules.oulu.fi/isbn9514264266/html/x325)

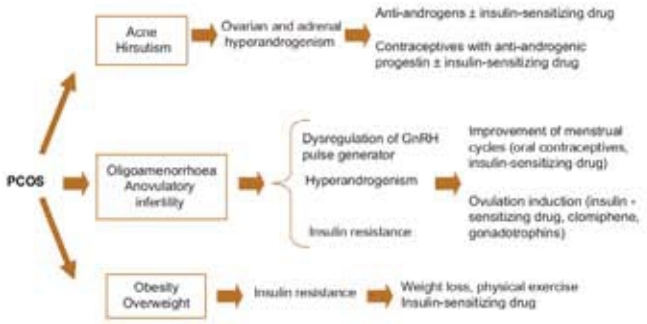


2. **Excluding related androgen excess of ovulatory disorders**

Ovulatory dysfunction may result from thyroid dysfunction and patients with insulin resistance do not necessarily have PCOS. Patients with menstrual cycle disturbance and insulin resistance need to be examined for simultaneous signs of hyperandrogenism. The probability of having PCOS increases if a patient has polycystic ovaries together with ovulatory dysfunction with or without androgen excess.

Treatment of PCOS is based on its underlying aetiology and on the presenting symptoms, as shown in Figure 2.

Figure 2: Management of the related features of PCOS



CONCLUSION

Research studies show that PCOS is not merely an endocrine disorder, but it also affects the hormonal, metabolic and psychosocial aspects which may have long-term consequences on the patient's quality of life.

Apart from causing immediate morbidities such as chronic anovulation, menstrual irregularity and infertility during the reproductive years, PCOS may also precipitate psychological and emotional distress, cardiovascular disease and the metabolic syndrome, Type II diabetes mellitus as well as endometrial and ovarian cancer and therefore any woman with possible PCOS requires investigation and treatment.

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TOWARDS NEW HORIZONS

The German - Maltese Medical Society's main aim is to promote closer ties between Germany and Malta in the medical field. In 2013, in collaboration with the Rotes Kreuz Krankenhaus (Red Cross Hospital)* in Kassel (Hesse) the GMMS managed to send nine Maltese medical students for Summer elective periods to this hospital. It was a great success and we had a very positive feedback, both from the medical students and from the consultants and the Red Cross Hospital administration in Kassel. The students were part of the hospital's medical and surgical teams and were given hands-on experience in the wards, operating theatres and the A&E department. They were also given afternoon lessons in German and the accommodation, as reported by the students, was excellent. They were even given a small personal stipend by the Red Cross Hospital. A big thank you goes to all who were involved.

This year we are repeating this set-up. However the medical students will first undergo a crash course in German, between February and April at the German-Maltese Circle headquarters (Messina Palace, Valletta) here in Malta. We thank Mr Victor Sammut from the German-Maltese Circle organizing this language course, as well as the Maltese Government and Dr Evarist Bartolo, Minister for Education, who agreed to cover all the expenses of the language course, text-books and the examination fees. This surely is an excellent way forward.

The German - Maltese Medical Society does not stop here. Discussions have been opened with the Postgraduate Medical Training Centre to explore:

1. the possibility for some of our newly - qualified doctors to undergo the Foundation Studies at the Rotes-Kreuz-Krankenhaus in Kassel.

The old and new new board of GMMS

2. the possibility for our postgraduate trainees to undergo a year or two of their postgraduate studies in Germany under the auspices of the University of Göttingen** (Hesse).
3. conjoint medical research and further training and exchange of our specialists in particular medical fields.

The discussions are currently at a level of a memorandum of understanding and we thank Dr Ray Galea, Lead coordinator of the Postgraduate Medical Training Centre, as well as Mr Michael Gribner and Mr Christian Collard from the Red Cross Hospital for their tremendous effort and valuable work.

Finally, I would like to mention that Dr Thomas Stöcker from Bremen, Germany, who is the Honorary Consul General of Malta, will be delivering a talk on "Rapid Hypnosis Induction Techniques in Dentistry" on Friday 11th April 2014 at 19.00 hrs at the German -Maltese Circle, Messina Palace -141, St Christopher Street, Valletta VLT 1465, Malta. All those interested are welcome to attend.

Dr Anthony Zammit M.D. - Facharzt für Chirurgie
President of the German-Maltese Medical Society
www.germanmaltesecircle.org/gmms.htm

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RESOLUTIONS OF A PHARMACIST FOR 2014

MPSA

Year in year out we try to do resolutions at the beginning of the year, some of which we have managed to adopt in our daily lives and others we ignore or find impractical, after all.

The following suggestions are a reminder for professionals.

- Take your time to dispense any medication with care. This should include a thorough explanation of how it should be administered, the time of day to be taken, diet considerations, and any precautions which the patient should be made aware of such as when taking other interacting medications or when there are co-morbidities.
- Discuss with the patient any health-related and social issues which might have an impact on their daily activities.
- Assist the patient to achieve cost-effective care.
- Proactively promote and support healthy lifestyles via education programmes including screening services.
- Rechecking a prescription is never a waste of time.
- A pharmacist is part of a multidisciplinary team; one should not hesitate to ask for advice or refer when needed.

IS THERE A ROLE FOR GENETIC RISK PREDICTION STUDIES IN TYPE 2 DIABETES?

NIKOLAI P PACE

ABSTRACT

Type 2 diabetes develops from the interaction between non-genetic (environmental/lifestyle) and genetic factors. One of the challenges of personalized genomics is the prediction of disease risk. This review examines the challenges of risk prediction studies and the barriers to their implementation in the clinic.

INTRODUCTION

The genetic study of common complex disease has undergone a massive transformation following the launch of genome-wide association scans (GWAS). These have greatly enhanced our knowledge on the contribution of common genetic variation in multifactorial diseases. Furthermore, the cost and timeframes necessary for whole genome sequencing has continued to diminish. Thereby, the endeavor of sequencing entire genomes has now shifted from being the sole realm of international consortia to lying within the technical capability and budgetary constraints of individual academic and research institutions.

FROM LABORATORY BENCH TO CLINICAL CARE

Undeniably, the genomics revolution has lead to the identification of hundreds of loci that are associated with clinical phenotypes or disease states. Yet the 'bench to bedside' translation from genomic discovery to clinical practice is an obscure and often controversial field that represents a major challenge to physicians and researchers alike. Many acknowledge that such a transition requires a significant shift in paradigm from the traditional Mendelian genetics approach. As the systems biology approach to complex disease becomes more vital to our understanding of human physiology, it is apparent that the contribution of single genes considered in isolation is relatively minor[1]. Instead epigenetic, gene-gene and gene-environment interactions critically underlie the etiology and pathogenesis of multifactorial diseases. Contrastingly, industrial ventures have sprung up that make use of genomic data to provide risk prediction information to individuals about health, disease and even behavioral traits. Companies like 23andMe (www.23andme.com) daringly claim that "23andMe can help you discover how your genes may affect your chances of developing various diseases and conditions, as well as traits such as athletic ability"[2]. Such bold and over-enthusiastic predictions regarding personalized medicine contrast with those of genome researchers and merit careful scrutiny[3].

RISK PREDICTION MODELS IN TYPE 2 DIABETES

Type 2 diabetes mellitus (T2DM) is a common multifactorial disease caused by the complex interplay between genetic and non-genetic (environmental/lifestyle) factors. It is highly heritable, with the relative risk for the disease in individuals with a family history being two- to six-fold higher compared to individuals without a family history of T2DM[4]. As a number of polymorphisms at various loci have been associated with T2DM, investigators have questioned whether combinations of risk alleles can be used to construct genetic risk scores for an earlier identification of individuals at risk.

CLINICAL RISK PREDICTION

Despite evidence that early lifestyle or pharmacological interventions can prevent or delay the development of the disease, the prediction of risk of new-onset T2DM is not part of routine clinical practice[5]. Two currently available risk prediction scores are based on demographic, anthropometric and biochemical data. The Cambridge T2DM risk score[6] is based on age, gender, family history, BMI and smoking status, and the Framingham offspring T2DM risk score[7] incorporates fasting blood glucose and lipid profile parameters into risk calculation. The two risk prediction algorithms provide a reasonable measure of discrimination of incident cases of T2DM, with area under the curve (AUC) values of 0.75 and 0.85 respectively. Furthermore, the addition of non-routinely measured indices of glucose metabolism, such as fasting plasma insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR) and a two hour oral glucose tolerance test, does not improve T2DM risk prediction[8].

GENOTYPES ARE ATTRACTIVE BIOMARKERS OF DISEASE RISK

Genotypes are appealing as disease biomarkers as they do not change with and are independent of age. Technological advances continue to improve on genotyping efficiency and throughput and offer the ability to multiplex single nucleotide polymorphism (SNP) assays in combination with high fidelity. Genotypes offer the intriguing prospect of risk determination from young age groups, where, in the light of cardiovascular disease prevention, earlier intervention has the maximum beneficial effects.

GENETIC RISK PREDICTION

The identification of genotypes that confer risk in T2DM and their incorporation into robustly validated risk-scoring algorithms based on phenotype has long been considered as the 'Holy Grail' of T2DM genetics. Relatively few studies exist that investigate the application of genetic risk scores in predicting T2DM, either as case-control or longitudinal follow-up studies. In all studies, irrespective of how many, or which risk loci were considered, and irrespective of whether genetic scores were weighted or not, the salient conclusion is that individuals with more risk alleles were at greater risk than those with fewer risk alleles. Hivert *et al* developed a genetic risk score using 34 T2DM-associated loci in over 2,800 individuals from different ethnic backgrounds representative of the US population[9]. In a three-year follow-up study, they demonstrated that higher values of a weighted genetic risk score were associated with increased risk of progression to T2DM. The study also reported that in individuals with high genetic risk scores, intensive lifestyle intervention was associated with higher incidence of regression to normal glucose regulation. On the other hand Meigs *et al* investigated a genetic score based on 18 T2DM-associated loci in over 2,000 individuals from the Framingham Offspring Study which were followed for twenty-eight years. They report that genetic risk scores predicted new cases of T2DM, with a 12% increase in relative risk of disease per risk allele[10]. Weedon *et al* reported similar findings using an unweighted genetic score constructed from just 3 common highly-replicated variants[11]. Similarly, Lyssenko *et al* reported on genetic risk scores using 16 T2DM-associated loci[12]. In all of these and other studies, the results showed that combinations of risk alleles can be used to identify a gradient of genetic risk that has a better predictive capacity than single polymorphisms considered in isolation. Despite the established association between the number of variants and disease risk, genetic risk scores in isolation offer poorer discriminatory capacity (AUC of 0.55 to 0.68) when compared to clinical risk prediction algorithms[13]. Interestingly, the discriminatory capacity of genetic risk scores does not correlate with the number of SNPs included in the risk score. The highest AUC (0.68) value was reported in the Botnia study that considered 11 SNPs in a prospective study design[14], and the lowest AUC value (0.55) reported in the FINDRISC study utilised the same 11 SNPs and an additional 8 polymorphisms in a cross-sectional study design[15]. The various published risk prediction studies also differ in the genetic variants included in their risk models. Since its discovery, the great majority of studies have included TCF7L2 in the list of risk-conferring variants. This gene has been hailed as one of the biggest success stories of T2DM genetics[16], as common variants in this gene have marked and reproducible effects on disease risk. Since its initial discovery by the deCODE investigators in 2006 in an Icelandic population[17], the role of TCF7L2 in T2DM risk has been replicated in various Caucasian[18] and non-European cohorts[19]. The majority of investigations have also included

TREATMENT WITH METFORMIN AND INTENSIVE LIFESTYLE INTERVENTION WAS EFFECTIVE AT REDUCING THE RISK OF DIABETES INCIDENCE AT ANY LEVEL OF GENETIC RISK

genetic variants in SLC30A8, IGF2BP2, PPAR-gamma and KCNJ11. Most of the other SNPs are included in one or two models only, so there is considerable heterogeneity in the existing genetic risk models for T2DM.

GENETIC RISK SCORES – WOULD THEY MAKE A DIFFERENCE?

Notwithstanding the academic interest in genetic risk scores, their potential translational clinical application in risk prediction remains to be determined. Prospective studies have determined that the commonly measured clinical risk factors of T2DM are powerful harbingers of T2DM risk. The addition of genotype data to these risk factors have added little useful information to risk prediction in populations at risk. Phenotypic risk factors, in particular obesity and adiposity indices, together with family history of T2DM are simple, inexpensive and easily measured clinical risk factors that are superior to any presently known genetic risk factors in disease prediction. Treatment with metformin and intensive lifestyle intervention was effective at reducing the risk of diabetes incidence at any level of genetic risk[9]. In a prospective investigation that compared a 20-allele genetic risk score to the Cambridge and Framingham T2DM risk scores, Talmud *et al* concluded that the addition of genotype data to phenotype-based risk models did not improve discrimination between T2DM cases and controls[8]. Similarly, the recent CARDIA study (Coronary Artery Risk Development in Young Adults) concluded that genotype score does not improve prediction over routine clinical measurements[20].

THE WAY FORWARD

A number of requirements must be fulfilled for T2DM genetic risk prediction in order for it to successfully achieve the bench to bedside transition:

- Clinical models comparable to the existing cardiovascular risk scores must be available to guide treatment regimes. For example, the established Framingham Cardiovascular Risk Scores for coronary heart disease risk prediction are used to guide LDL-C targets in individual patients based on their ten-year risk of disease[21];
- Expense-conscious health care services also require genotyping to be carried out within reasonable costs and timeframes;
- Genetic risk scores should be developed using representative samples of the populations in which they will ultimately be applied to target prevention;
- Study methodology significantly impacts on the discriminatory capacity of genetic risk scores. Prospective follow-up studies are best suited for genetic risk prediction[13].

CONCLUSION

Clinicians should always advocate the maintenance of a healthy weight and balanced diet as the cornerstone of T2DM prevention - irrespective of one's genotype. However, genetic risk scores could be used to identify subgroups with particular elevated risk for targeted intensive risk modification programs or pharmacotherapy. Such programs are resource-intensive, and in healthcare systems affected by finite resources, could offer a personalized approach to risk prevention in selected individuals. Nevertheless the clinical importance of excess adiposity and obesity as the principal functional risk factors in T2DM risk determination and disease progression remains undisputed.

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BRUGADA SYNDROME AND SUDDEN CARDIAC DEATH

SAMUEL MEILAK & MARK SAMMUT

ABSTRACT

A recently discovered cause of sudden cardiac death, Brugada syndrome is a conductivity disorder in structurally normal hearts. We present here a case of an incidental Brugada sign, outlining the clinical and pathophysiological findings in Brugada syndrome. We also give an account of the published guidelines regarding implantable cardioverter-defibrillators and highlight the importance of educating clinicians and the public alike in the management of Brugada syndrome.

CASE PRESENTATION

A 49 year old gentleman, with no relevant medical history, presented with epigastric discomfort associated with sweating but no nausea or vomiting. He was haemodynamically stable and clinical examination proved unremarkable. The electrocardiogram (ECG) showed ST segment elevation in the right chest leads whilst serial troponin levels were within normal range. Coronary angiogram showed normal contractility and no significant coronary artery disease. The working diagnosis was of epigastric discomfort secondary to dyspepsia, with the Brugada sign being an incidental ECG finding. The plan was for this patient to be managed expectantly and with regular ECGs.

HISTORY OF BRUGADA SYNDROME

The first paper on Brugada syndrome described eight cases and was published in 1992. It describes the first documented case which occurred in a three year old Polish boy who in 1986 presented with multiple episodes of loss of consciousness; he was resuscitated repeatedly by his father. The child's sister had died suddenly at two years of age. The ECGs of the both siblings were very similar and abnormal.

In recent years there has been an exponential increase in the number of cases reported[1]. Recent genetic profiling seems to indicate that Brugada syndrome is a primary conduction disorder[2].

BRUGADA SYNDROME

This channelopathy is characterised by sudden death associated with one or more of several ECG patterns i.e. incomplete right bundle branch block (RBBB); ST elevation; and J-point elevation in the anterior precordial leads (V_1-V_3). Three different types have been described, classified according to their characteristic ST segment abnormalities in leads V_1-V_3[3]. It is debatable whether the RBBB is real or reflecting early repolarisation of the right ventricular epicardium. In some but not all cases this resolves after normalisation of the ST segment. In addition, the PR interval is usually increased, reflecting a prolongation in the H-V interval.

There is a propensity for life-threatening ventricular arrhythmias, with the complete syndrome being characterised by episodes of fast polymorphic ventricular tachycardias (VT). These may range from self-limiting runs causing syncopal attacks to ongoing arrhythmias causing a full blown cardiac arrest and sudden cardiac death.

The above mentioned abnormalities occur in the setting of a structurally normal heart.

PATHOPHYSIOLOGY

Recent research has implied a loss-of-function mutation of the SCN5A gene in about 10-30% of patients with Brugada syndrome. This affects the cardiac voltage-gated sodium channel ($Na_{v1.5}$) leading to a reduction in the sodium current (I_{Na}) available during the phases 0 (upstroke) and 1 (early repolarisation) of the cardiac action potential.

One of the hypotheses which have been put forward to explain the underlying mechanism is the 'Repolarisation-defect theory'. It proposes that there is an increased contribution of the transient outward current (I_{to}) to the action potential waveform in right ventricular epicardial cells compared to endocardial cells (giving a more prominent notch in the action potential of the former). This difference is accentuated by a decrease in I_{Na}, creating a voltage gradient during repolarisation and the characteristic morphology of ST elevation[2]. Another hypothesis explains the ECG findings as a reflection of disordered conduction (delayed activation and slow conduction) in the right ventricle, mainly the outflow tract. This is known as the depolarisation hypothesis.

DIAGNOSIS

A patient may be completely asymptomatic and said to have the Brugada sign. Those suffering from Brugada syndrome typically present with syncope but sudden cardiac death may also occur, commonly during sleep. Physical examination is unremarkable whilst there is usually a strong family history of sudden cardiac death.

INVESTIGATIONS:

1. ECG Changes: ST elevation ≥ 2mm in ≥ 1 lead from V1-V3 with typical morphology, with an associated RBBB pattern.
2. Imaging, including angiography shows no underlying structural or coronary disease.

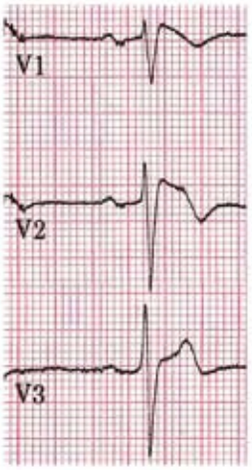

Figure 1: ECG from our patient showing typical Brugada pattern

3. Stress tests: Symptoms and ECG findings are not usually reproducible with exercise; interestingly, ST elevation normalises with increase in heart rate on exertion[4].

CRITERIA FOR THE DIAGNOSIS OF BRUGADA SYNDROME HAVE BEEN ESTABLISHED AS FOLLOWS[5]:

Major criteria

- Presence of ECG marker in structurally normal hearts
- Appearance of ECG marker after administration of sodium channel blockers

Minor criteria

- Family history of sudden cardiac death
- Syncope of unknown origin
- Documented ventricular tachycardia/fibrillation
- Genetic mutation of ion channels
- Positive programmed electrocardiostimulation test on VT / VF

MANAGEMENT

Implantable cardioverter-defibrillator implantation is the mainstay of treatment. Expert consensus recommendations have recently been published by Priori SG et al[4].

Table 1: Expert consensus recommendations on Brugada Syndrome therapeutic interventions

Class I	ICD is recommended in patients with a diagnosis of BrS who: a) are survivors of a cardiac arrest, and/or b) have documented spontaneous sustained VT with or without syncope
Class IIa	ICD can be useful in patients with a spontaneous diagnostic Type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias
Class IIb	ICD may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients)
Class III	ICDs are not indicated in asymptomatic BrS patients with a drug-induced type 1 ECG and on the basis of a family history of sudden cardiac death alone

SUDDEN CARDIAC DEATH

With an annual incidence of 0.1-0.2% , sudden cardiac death claims seven million lives per year worldwide. Males are affected three times as much, with a peak incidence between 45 and 75 years. The commonest cause is coronary artery disease, followed by cardiomyopathies and channelopathies. The most common cardiomyopathies are dilated, hypertrophic, arrythmogenic right ventricular, restrictive and left ventricular non-compaction. Channelopathies include Brugada syndrome, long and short QT syndromes, idiopathic VF and short-coupled variant of Torsades de Pointes[6].

Figure 2: Chain of Survival[7]

CONCLUSION

The educated eye should look out for the Brugada sign in every electrocardiogram, in order to diagnose and appropriately manage these patients. In addition, the chain of survival following cardiac arrest should be well known to all.

ABBREVIATIONS

BrS - Brugada Syndrome
ECG - Electrocardiogram
ICD - Implantable cardioverter-defibrillator
RBBB - Right bundle branch block
SCD - Sudden cardiac death
VT - Ventricular tachycardia
VF – Ventricular fibrillation

REFERENCES CAN BE ACCESSED ON THE MAGAZINE

THE MED-LIFE CRISIS

ALEXANDER GRIMA

The medical student life feels much akin to being on the wrong side of a firing squad. Singled out by some impatient consultant with an impossible question, we feel the eyes of fellow students, doctors and patients alike fall upon us and we die a little bit inside. All the knowledge we so avidly absorbed the night before vaporises instantly in the flashpoint and we're left dumb, searching frantically for any cue, feeling all alone in the world, hoping and dreading at the same excruciating time for the axe to fall.

In truth you can't be blamed for thinking that talking to one of us students might be the most depressing experiences you'll ever have to go through. We grumble on Mondays' about lectures and moan on Fridays about cancelled tutorials. Nothing is safe from our cynicism! But much of this is in fact just a smoke screen. If you just listen long enough you'll eventually hear each and every one of us say, "This is exactly where I belong."

And no wonder! We've become addicted to the nerdy highs we get when we put on scrubs for the first time or get that ankle jerk just right! Every patient and every MRI still has that power to evoke mental oohs and aahs. We can't help to be drawn in, to fall in love with the mystery of the human body and the unpredictable nature of the human mind, although obsessively fitting weird diseases with whatever vague symptoms we wake up with in the morning might become a common side effect …

Despite all these amazing things, we still moan and grumble. Perhaps it's the only way we know how to cope with the immense responsibility. Maybe it's an instinctive drive to keep us grounded in reality. Though one thing is for certain … once we taste this life, there is no going back!

QUIZ

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ALISON BRINCAT B.PHARM(HONS) MSC (PHARMACY) M.PHARM IS THE LUCKY WINNER OF THE MEDICAL LANGUAGE TRANSLATOR BOOK PUBLISHED BY MMSA. SHE WAS THE 5TH PARTICIPANT WHO REPLIED CORRECTLY TO THE QUESTION, 'IF A PREVIOUS DIABETIC PINK CARD HOLDER OPTED FOR A DIABETIC YELLOW CARD BEFORE 1ST JUNE 2012 CAN THE PATIENT REVERT TO THE PINK CARD? YES OR NO?' PUBLISHED IN ISSUE 5/13. THE CORRECT ANSWER WAS YES.

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UNFORTUNATELY THERE HAS BEEN NO WINNER. THE CORRECT QUESTION OF THE FOLLOWING QUESTION 'WHICH FAMOUS STAR TREK DOCTOR DOES DR. PULASKY EMULATE AND IN WHICH STAR TREK SERIES DOES THIS OTHER CHARACTER APPEAR?' SHOULD HAVE BEEN DR LEONARD MCCOY APPEARING IN THE STAR TREK *THE ORIGINAL SERIES*.

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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. Capsules must not be swallowed. 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. **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 124, Valletta, VLT 1000 Malta. Tel: +356 22983217/+35621222872. 2013-MT-ONB-09-Sep-2013

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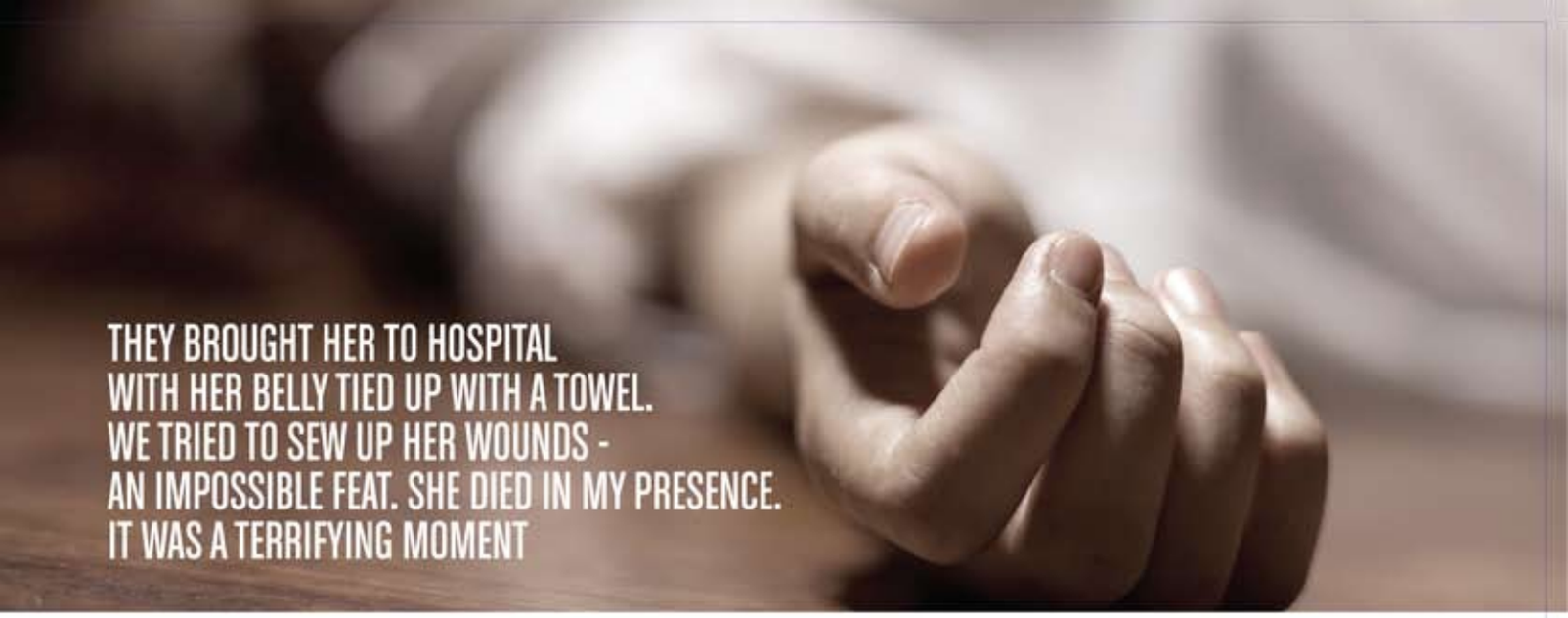
MARIKA AZZOPARDI

ANAESTHESIA AND SO MUCH MORE BESIDES...

I meet Dr Nazzareno Azzopardi just three days before his graduation day. And he's 75 years old ... a specialist anaesthetist whose medical profession has given him more than his fair share of stories to tell. As he prepares to graduate as a Legal Procurator, he sits in the clinic in his suit and tie, and recounts just a fraction of his life to me. Here is what I find out about him...

He still practises as a doctor, on a voluntary basis in a home for the elderly, some patients being younger than himself. It is his way of keeping in touch with the medical profession and contributing to the greater good. It all began way back in 1961, when he graduated as a medical doctor, spent the regular three-year stint working at St Luke's Hospital and then decided it was high time to specialise. "I was at odds between two choices - obstetrics and anaesthesia. Finally, my marks decided for me. I placed first in anaesthesia and was highly encouraged by one of my tutors - Dr Charles Podesta - an exceptional man." So anaesthesia it was. He was awarded a Diploma in Anaesthesia in 1965, after which he won a Council of Europe scholarship in 1970, specialising in Paediatric Anaesthesia at the Karolinska Sjukhuset of Stockholm and at the Clinica Gaslini in Genoa. He spent time in London in 1975 to gain a Fellowship with the Faculty of Anaeasthetists of the Royal College of Surgeons of England.

"By 1976 I had been appointed Consultant Anaesthetist and Head of the Gozo Anaesthesia Department by the Maltese Government. By 1977 I was a lecturer in Anaesthesia at the University of Malta, but that was the same year of the infamous doctors' strike. It was an extremely trying period of my life. I proudly avoided the strike, since I always considered patients as my first priority. I remember discussing my decision with the hospital chaplain at the time, and he had advised me towards making a moral decision. In the end, I was one of the only 54 doctors who remained working with the government of the time. We kept things going and it was definitely not easy. I had a patrol boat constantly at my service, ferrying me to and from Malta and Gozo, covering all the operations that needed to be done. Eventually I ended up heading the Anaesthesia Department at St Luke's Hospital, as well as setting up the



THEY BROUGHT HER TO HOSPITAL WITH HER BELLY TIED UP WITH A TOWEL. WE TRIED TO SEW UP HER WOUNDS - AN IMPOSSIBLE FEAT. SHE DIED IN MY PRESENCE. IT WAS A TERRIFYING MOMENT

Intensive Care Unit - posts I held until retirement in 1999." His work, in collaboration with several foreign experts, transformed the new ITU into a fully functional and professional unit, which eventually led to the development of the SCBU.

It was this position that led him to witness several terrible fatalities caused by violent episodes of violence imprinted in history. Dr Azzopardi recalls the day Karin Grech was assassinated. "They brought her to hospital with her belly tied up with a towel. We tried to sew up her wounds - an impossible feat. She died in my presence. It was a terrifying moment. All doctors who had not participated in the strike were worried about their life and their families' safety. I myself received threats but carried on nonetheless. My wife stayed with her mother for some time, taking along the children to safeguard them. Of course, Karin's demise led to the creation of Karin Grech Hospital which served its purpose well for many successful years."

At a distance of so much time, Dr Azzopardi's face still darkens as he recalls these incidents. By that time, his family was complete. He and his wife Grace have four children, boys, now grown adults. One is a pilot, one is a vet, one is a businessman and one is an orthopaedic consultant surgeon. Being a family man at heart, Dr Azzopardi's face lights up again, this time proudly, on mentioning his family.

Another episode that marked his medical experience was the Egyptair hijack in 1985. "We were apprehensively following the minute-to-minute events as they unfolded during those nerve-wracking 24 hours. As head of the Intensive Care Department, I was part of the team responsible for the immediate care and medical attention given to anybody injured during the hijack. After the attack happened, we were presented with a large number of seriously injured people, most of which had to be operated on immediately. I remember, at the time, our present Speaker of the House of Representatives, Dr Angelo Farrugia, was a Police Inspector. He approached me as we prepared to start operating these victims, informing me that one of the men we were to operate on, was a hijacker. I did not know who was who. We proceeded with the operations which had to be carried out. Eventually, there were 58 victims in all after that fateful event."

In 1992 Dr Azzopardi decided it was high time he take a sabbatical. To rest? Far from it. With the consent of wife and children, he set off to Papua New Guinea to work as a Lay Missionary. It was a momentuous year, as evidenced by his book *Mission Experience - Papua New Guinea*, in which he documents salient moments of his experience, including his several brushes with malaria.

Referring once again to Dr Angelo Farrugia, Dr Azzopardi says the man was an inspiration to take up Law in later years. "With the last pay packet received at age 61, I knew I needed something to fill my time. I resumed study by taking up Theology up to Masters level. Then during my last year in Theology, I started Law. With Theology, the evening classes were shared by a good number of adult students. With Law, it was different. At first it felt strange to be a full-time student once more, especially since I was sharing my studies with people so much younger than myself. At first I kept to myself a lot, but soon integrated and became friends with all."

It has certainly been an eventful ride for Dr Azzopardi. As he prepares himself for his umpteenth graduation, he is not sure what comes next... more study perhaps? Dr Azzopardi does not comment but as is typical of such a man, the last word is not about himself... "May I make a final comment? Through all these years I have appreciated the constant collaboration of dedicated nurses. We tend to disregard nurses as appendices to doctors, when in reality they are key collaborators who deserve all the respect in the world."

PIERRE VASSALLO

BREAST CANCER IMAGING: DUCTAL CARCINOMA IN-SITU (DCIS) PART II

DCIS is rarely seen on US, where it may appear as a microlobulated mass with mild hypoechogenicity, ductal extension, and normal acoustic transmission.

Recent studies conducted at higher spatial resolution MRI have increasingly been performed to screen higher-risk women as well as to evaluate extent of disease. The sensitivity of MR imaging for detection of DCIS has been shown to be higher for high-grade and intermediate-grade DCIS as compared with low-grade DCIS (98%, 91%, and 80%, respectively). Overall, MR imaging is more sensitive than mammography in the detection of all grades of DCIS. Over the past decade, studies have shown that the sensitivity of MRI for DCIS has improved significantly and is much higher than that of mammography (92% vs 56%, respectively).

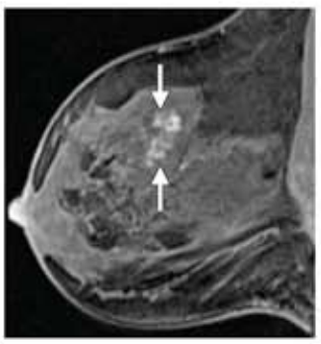


Figure 9: High-grade DCIS in a BRCA2-positive woman appearing as a 2.5-cm area of linear, clumped NME (arrows) on sagittal postcontrast T1-w scans.

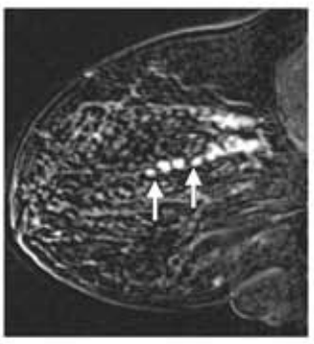


Figure 10: Intermediate-grade DCIS seen on contrast-enhanced T1-w scans as multiple round areas of NME distributed in a linear distribution.

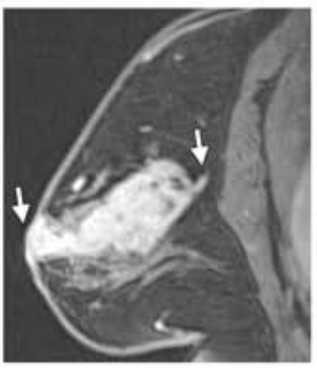


Figure 11: Intermediate-grade DCIS seen on contrast-enhanced T1-w scans as a segmental area of enhancment (arrows).

DCIS most commonly appears on contrast enhanced T1-weighted MRI scans as an area of Non-Mass Enhancement (NME) (Fig 9), which is an area of enhancement without evidence of a mass or focal lesion on non-enhanced scans. DCIS manifests as NME in 60–81% of cases, as a mass in 14–41% of cases or as a focal lesion on non-enhanced scans in

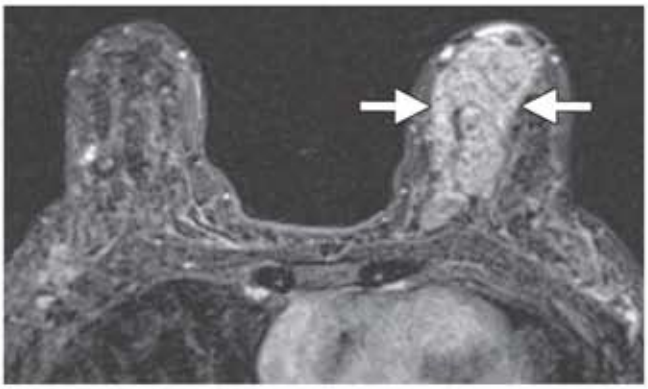


Figure 12: Intermediate-grade DCIS seen on contrast-enhanced T1-w scans as a regional area of enhancment (arrows).

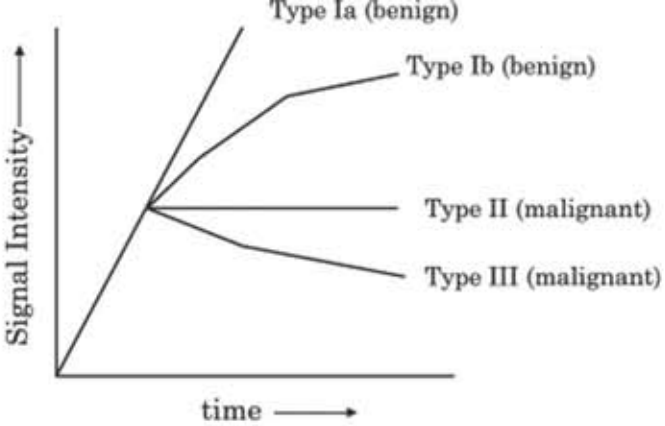


Figure 13: Dynamic-contrast enhancement patterns (Time/enhancement curves): the presence of a wash-out phase (i.e. a drop in signal intensity after a rapid initial contrast uptake – Type 2 or 3) is indicative of malignant disease.

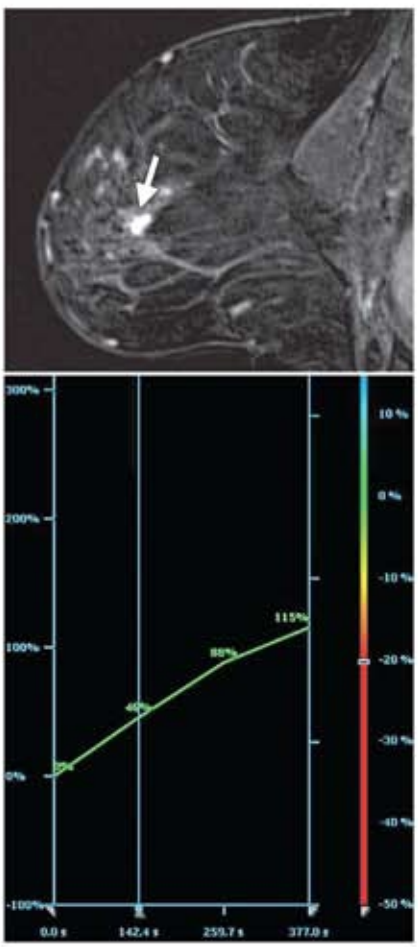


Figure 14: High-grade DCIS seen on a sagittal postcontrast subtraction image (top) shows an area of clumped NME measuring up to 2 cm (arrow) that demonstrated Type 2 enhancement kinetics (bottom).

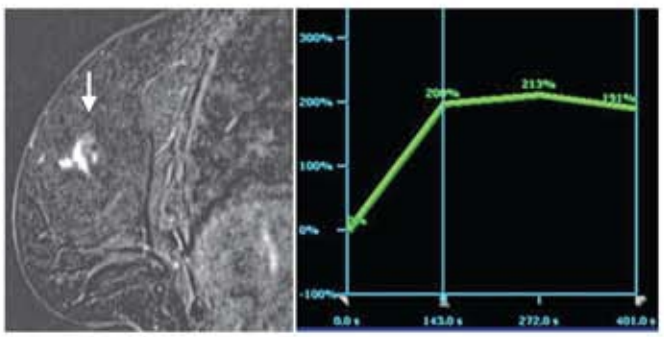


Figure 15: High-grade DCIS appearing as a nodular-enhancing lesion on contrast-enhanced T1-w images. Enhancement kinetics (Type 1) was more in keeping with a benign lesion. An increase in size of the lesion was noted compared to a previous MRI scan, which prompted biopsy.

1–12% of cases. Subtraction of pre-contrast from post-contrast enhanced images significantly improves lesion conspicuity. DCIS is usually not visible on non–contrast material–enhanced T1-weighted images or on non–fat-saturated or fat-saturated T2-weighted images because it is masked by the normal breast parenchyma. DCIS may sometimes appear bright on T2-weighted images because of either ductal secretions or necrosis.

DCIS on contrast enhanced T1-w scans may have a linear (Fig 10), segmental (Fig 11) or regional (Fig 12) distribution.

Kinetic assessment of contast enhancement (time/enhancment pattern) is also helpful in distinguishing benign from malignant lesions with breast MRI. A wash-out pattern of contrast enhancment (loss of signal intensity following the uptake phase) is more indicative of a malignant lesion while persistent enhancement is usually seen in benign lesions (Figs 13 and 14).

DCIS may appear nodular or as a mass lesion, and kinetic studies are not always reliable in DCIS (Fig 15). Follow-up examinations may be required for equivocal lesions as a negative biopsy may be due to incorrect sampling. Nodular or mass lesions may have homogeneous, heterogeneous or rim-enhancement patterns; the heterogeneous enhancement patter is most common in DCIS.

The extent of DCIS is often underestimated at mammography because mammography does not usually reveal noncalcified DCIS. MR imaging has been shown to depict more accurately the extent of DCIS because of its ability to demonstrate noncalcified DCIS.

Of all imaging tools available, MR imaging has the highest sensitivity in the detection of DCIS. DCIS has a variety of MR imaging features that need to be recognised.

European Medicines Agency recommends that PROTELOS® remains available with further restrictions

Press Release
Suresnes France, 21st February 2014

Servier would like to inform healthcare professionals that the European Medicines Agency (EMA) has concluded its review of Protelos® benefits and risks, and has recommended maintaining the European Marketing Authorization with further restrictions of the indication[1] and monitoring recommendations.

The Committee for Medicinal Products for Human Use (CHMP), which has worked in close collaboration with the Pharmacovigilance Risk Assessment Committee (PRAC), has considered the current contra-indications[2] sufficient to minimise the cardiovascular risk. In addition, the CHMP has noted that available data do not show any evidence of an increased risk in patients who did not have a history of heart or circulatory problems.

In practice, cardiovascular risk monitoring of patients will be increased and information for healthcare professionals and patients will be strengthened.

The beneficial effect of Protelos® in preventing fractures, including in patients at high risk of fracture, is confirmed.

Under these conditions, the EMA considers that the benefit-risk ratio is positive and that Protelos® represents a necessary alternative in the treatment of osteoporosis.

Servier is informing all health agencies in countries where Protelos® is registered of these changes and is conducting further research to demonstrate the effectiveness of the new measures.
Servier will send detailed information to healthcare professionals informing them of the updated recommendations for use in the coming days and will also provide educational materials for prescribers and patients.

[1] Protelos® is now indicated in the treatment of severe osteoporosis in postmenopausal women and adult men, at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. In postmenopausal women, Protelos® reduces the risk of vertebral and hip fractures.

[2] Protelos® is contra-indicated in patients with established, current or past history of venous thromboembolic event, ischemic heart disease, peripheral arterial disease, cerebrovascular disease, and/or in case of uncontrolled hypertension or temporary or permanent immobilisation.

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A leading partner in osteoporosis research

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