THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

Volume 18, 2019 Issue 04 ISSN number 2313-8084

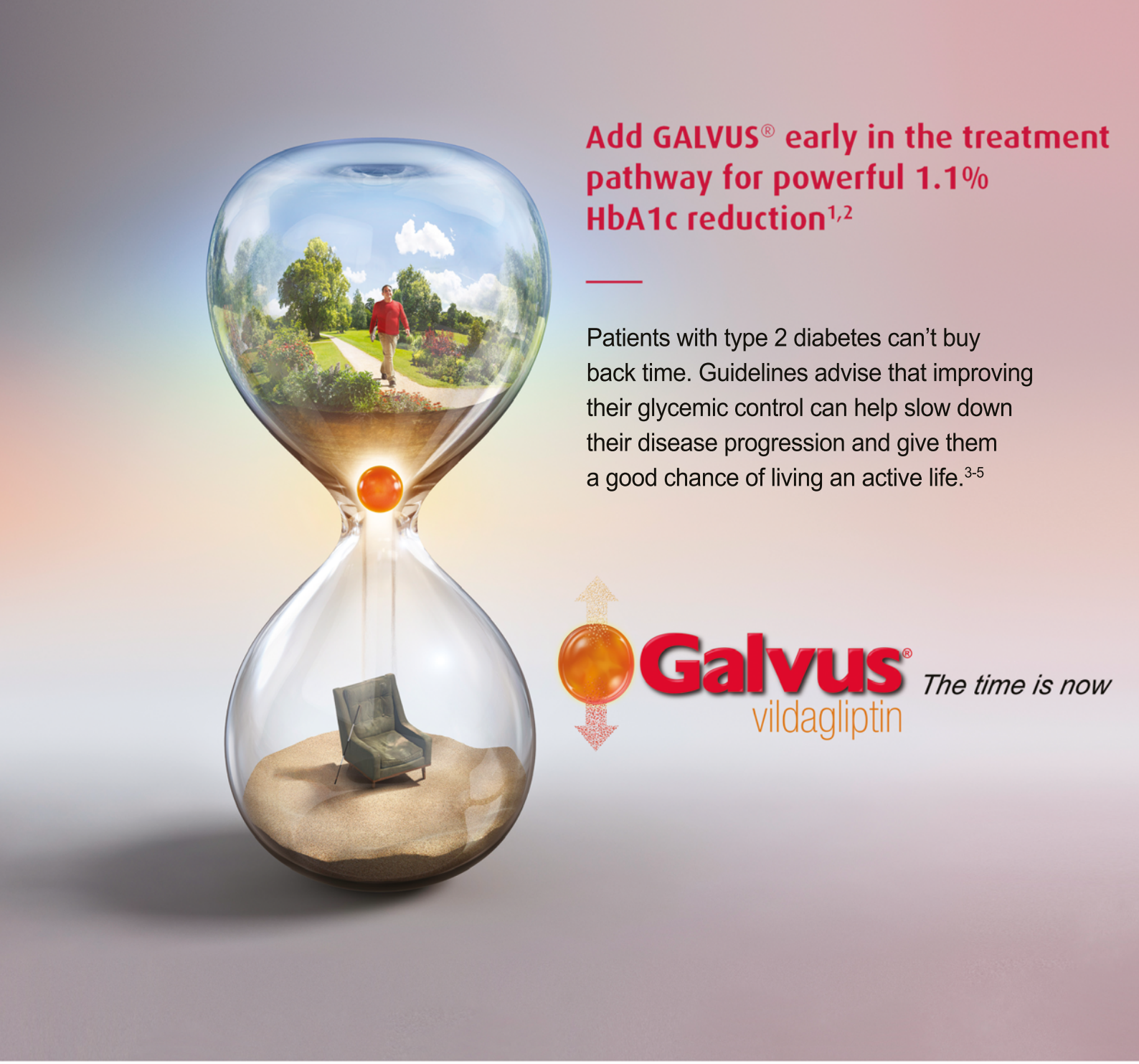
Virtual Reality in Healthcare...

Exploring New Realities!

Diagnosing common types of tremor in two shakes

Meeting Prof. Maurice Cauchi

Understanding the Breast Specialist's Jargon



Add GALVUS® early in the treatment pathway for powerful 1.1% HbA1c reduction[1,2]

Patients with type 2 diabetes can't buy back time. Guidelines advise that improving their glycemic control can help slow down their disease progression and give them a good chance of living an active life.[3-5]

Galvus® vildagliptin

The time is now

Galvus®

PRESENTATION: Each tablet contains 50 mg of Vildagliptin **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults: i) As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. ii) 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. iii) 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 metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea 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 dual combination with a sulphonylurea, the recommended dose is 50mg once daily in the morning. 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. 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. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. Galvus is not recommended for use in children and adolescents (< 18 years) as the safety and efficacy have not been established and no data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. No dose adjustments are necessary in elderly patients (≥ 65 years). **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 and Galvus should be used with caution in these patients. Galvus should be used with caution in patients with renal impairment. Galvus should not be used in patients with hepatic impairment. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class I-III treated with Vildagliptin is still limited. There is no experience with NYHA class IV and therefore use of Vildagliptin is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Exercise caution in patients with a history of acute pancreatitis. Patients with 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. **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. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors **ADVERSE REACTIONS:** Monotherapy: Common (>1/100 to <1/10): dizziness. Combination with metformin: Common: hypoglycaemia, tremor, headache, dizziness, nausea. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. For a full list of Adverse Reactions please refer to the SmPC. **LEGAL CATEGORY:** POM **PACK SIZES:** 28 tablets. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/003. **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 21222872. 2018-MT- GAL-26-APR-2018

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1. Novartis Europharm Ltd. Galvus Summary of Product Characteristics
2. Novartis Europharm Ltd. Eucreas Summary of Product Characteristics
3. Holman RR et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15):1577–1589.
4. Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38(1):140-149.
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Eucreas®

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. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma. Severe renal failure (GFR < 30 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. Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. GFR should be assessed before treatment initiation and regularly thereafter. 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 at the time of surgery under general, spinal or epidural anaesthesia and resumed no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. The IV administration of iodinated contrast agents can lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. 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. A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.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. The use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **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 due to an increased risk of lactic acidosis, iodinated contrast agents, 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 and products which can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop 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) angiodema, 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, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/021, EU/1/07/425/027. **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 21222872 2018-MT-EUC-23-APR-2018

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Galvus® vildagliptin

Eucreas® vildagliptin/metformin

MICROPLASTICS & NANOPLASTICS
IN THE MARINE ENVIRONMENT

EDITORIAL

I will start this editorial with some staggering numbers. Every year worldwide, more than 8,000,000 tons of plastic end up in our seas. In a business-as-usual scenario, this is expected to increase to 16,000,000 tons by 2030 and 32,000,000 tons by 2050. If no action is taken our seas are expected to contain 1 tonne of plastic for every 3 tonnes of fish by 2025, and by 2050, more plastic than fish by weight.[1]

Biodegradation of plastic is a process that results in total or partial conversion of organic carbon into biogas and biomass associated with the activity of microorganisms (bacteria and fungi) capable of using plastic as a carbon source.[2] This process is temperature-dependent and, in some cases, complete degradation can only be achieved above 50°C. Such conditions are rarely met in the marine environment. In addition, the polymers most commonly used (e.g. polyethylene & polypropylene) are not readily biodegradable; they are only subjected to weathering and fragmenting into micro- and nanoplastics; these remain in the environment for hundreds of years.

Microplastics are considered to comprise plastic particles ≤ 5mm which may fragment to secondary nanoplastics. These are generally considered to include plastics ≤ 100nm. The microplastics released in the sea primarily originate from laundering of synthetic textiles [which release fibre-forming polymers], tyre tread abrasion of car tyres & city dust [including abrasion of objects such as synthetic cooking utensils and abrasion of infrastructure such as building coatings].[1]

One overlooked consideration relates to the additives which are found in plastics such as stabilisers, plasticisers, flame retardants and pigments. It is estimated that approximately 225,000 tonnes of such additives are released into our seas annually. This number is envisaged to increase six-fold to 1.2 million tonnes per year by 2050.[1]

The micro- and nanoplastics enter the food-chain through their ingestion by zooplankton and small fish; studies have also identified sea-salt as an entry point.[3] On a side-note it is also worth noting that synthetic fibres have also been detected in beer, honey, sugar and tap water!

In the food-chain, the impact of nanoplastics and microplastics on humans is not well-understood. Studies have been advocated in the following areas:

- The effect of microplastic and nanoplastic ingestion and accumulation on the microbiome and on the embolization of small vessels, inflammation and immunoreactions;
- The amount of microplastics and nanoplastics in food and when these are transferred between trophic levels such as when fish products are used to feed poultry and livestock.

I wish to end this editorial with the following ponderation. A global study[4] published in 2017 presented the first global analysis of *all mass-produced plastic ever manufactured.* It revealed that approximately 9% has been recycled, 12% incinerated, and 79% accumulated in land-fills or the natural environment. Against this backdrop, we must talk the talk and walk the walk. Taking Japan as an example it managed to achieve 90% recycling of plastics by reducing drastically the production of **coloured** plastic bottles. Industry agreed to make transparent PET. Previously it produced blue, green and red plastic containers which, upon recycling, produced amber-coloured plastic which no-one wanted to re-use.

Everyone has the responsibility to be the guardian of future generations. We must ACT… now…

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2. World Economic Forum. The new plastics economy - Rethinking the future of plastics, 2016.
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MMSA Malta Medical Students' Association
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MADS Malta Association of Dental Students

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SEROXAT

The Anxiolytic Antidepressant:[1,2]

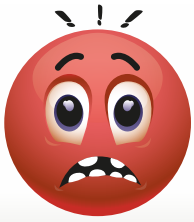
Major Depressive Disorder (MDD)[3]

Generalised Anxiety Disorder (GAD)[3]

Social Anxiety Disorder (SAD)[3]

Post -Traumatic stress Disorder (PTSD)[3]

Obsessive Compulsive Disorder (OCD)[3]



Panic Disorder[3]

Different indications require different dosage regimens. Please refer to the full SPC for more prescribing information.

SEROXAT ABRIDGED PRESCRIBING INFORMATION

Please refer to full Summary of Product Characteristics (SPC) before prescribing.

TRADE NAME: SEROXAT. ACTIVE INGREDIENT: Paroxetine. **PHARMACEUTICAL FORM:** Film-coated tablets, 20mg. **INDICATIONS:** Major Depressive Episode, Obsessive Compulsive Disorder, Panic Disorder with and without agoraphobia, Social Anxiety Disorders/Social phobia, Generalised Anxiety Disorder, Post-traumatic Stress Disorder. POSOLOGY: Administer once daily in the morning with food. Refer to full SPC for dosing information for specific conditions. Withdrawal symptoms seen on discontinuation of Paroxetine: abrupt discontinuation should be avoided. ***Elderly:*** maximum dose should not exceed 40mg daily. ***Children and adolescents:*** Should not be used. ***Renal/hepatic impairment:*** Dose should be restricted to lower end of dosage range. **CONTRAINDICATIONS:** Hypersensitivity. Should not be used in combination with MAOIs, thioridazine or pimozide. **PRECAUTIONS:** Treatment should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAOI; Do not use in children and adolescents under the age of 18 years; Suicidal thoughts or clinical worsening: an improvement may not occur in the first few weeks of treatment: patients should be closely monitored; Use of paroxetine has been associated with development of akathisia: most likely to occur within first few weeks of treatment: do not increase dose in these patients; Serotonin syndrome/ neuroleptic malignant syndrome may develop rarely: treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. Do not use in combination with serotonin-precursors; Use with caution in patients with a history of mania, severe renal and hepatic impairment, diabetes (there have been studies suggesting an increase in blood glucose levels may occur when paroxetine and pravastatin are co-administered) and in epilepsy; Drug should be discontinued if patients who develop seizures; There is little clinical experience of concurrent use with ECT; Use with caution in narrow angle glaucoma or history of glaucoma, patients with cardiac conditions or at risk of hyponatraemia; Caution when administered concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase risk of bleeding; Paroxetine may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen: concomitant use should be avoided; Withdrawal symptoms may occur on discontinuation of Paroxetine treatment. *Refer to full SPC for information on drug interactions*. **PREGNANCY/FERTILITY/LACTATION:** ***Fertility:*** SSRIs may affect sperm quality but this is reversible following discontinuation of treatment. ***Pregnancy:*** Use in pregnancy only when strictly indicated due to potential increased risk of cardiovascular malformations during the first trimester; symptoms such as respiratory distress, cyanosis, apnoea, seizures and other complications may occur in the neonate after maternal paroxetine use in later stages of pregnancy and increased risk of persistent pulmonary hypertension of the newborn (PPHN). ***Lactation:*** Use during lactation can be considered. **UNDESIRABLE EFFECTS:** ***Very Common (≥ 1/10):*** Nausea, Sexual dysfunction; ***Common (≥ 1/100, <1/10):*** Increases in cholesterol levels, decreased appetite, somnolence, insomnia, agitation, abnormal dreams (including nightmares), dizziness, tremor, headache, impaired concentration, blurred vision, yawning, constipation, diarrhoea, vomiting, dry mouth, sweating, asthenia, body weight gain; Increased risk of bone fractures in patients receiving SSRIs and TCAs; Common withdrawal symptoms include: dizziness, sensory disturbances, sleep disturbances, anxiety, headache. Adverse events from paediatric clinical trials: Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility were observed. ***Refer to full SPC for the full list of adverse reactions.*** **LOCAL PRESENTATIONS:** 20mg Tablets (by 30 tablets). MARKETING AUTHORISATION HOLDER: GlaxoSmithKline (Ireland) Ltd **MARKETING AUTHORISATION NUMBERS:** MA192/02501. **LEGAL CATEGORY:** POM. DATE OF PREPARATION: May 2019.

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

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

Alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal

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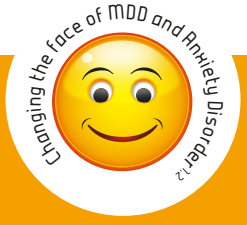

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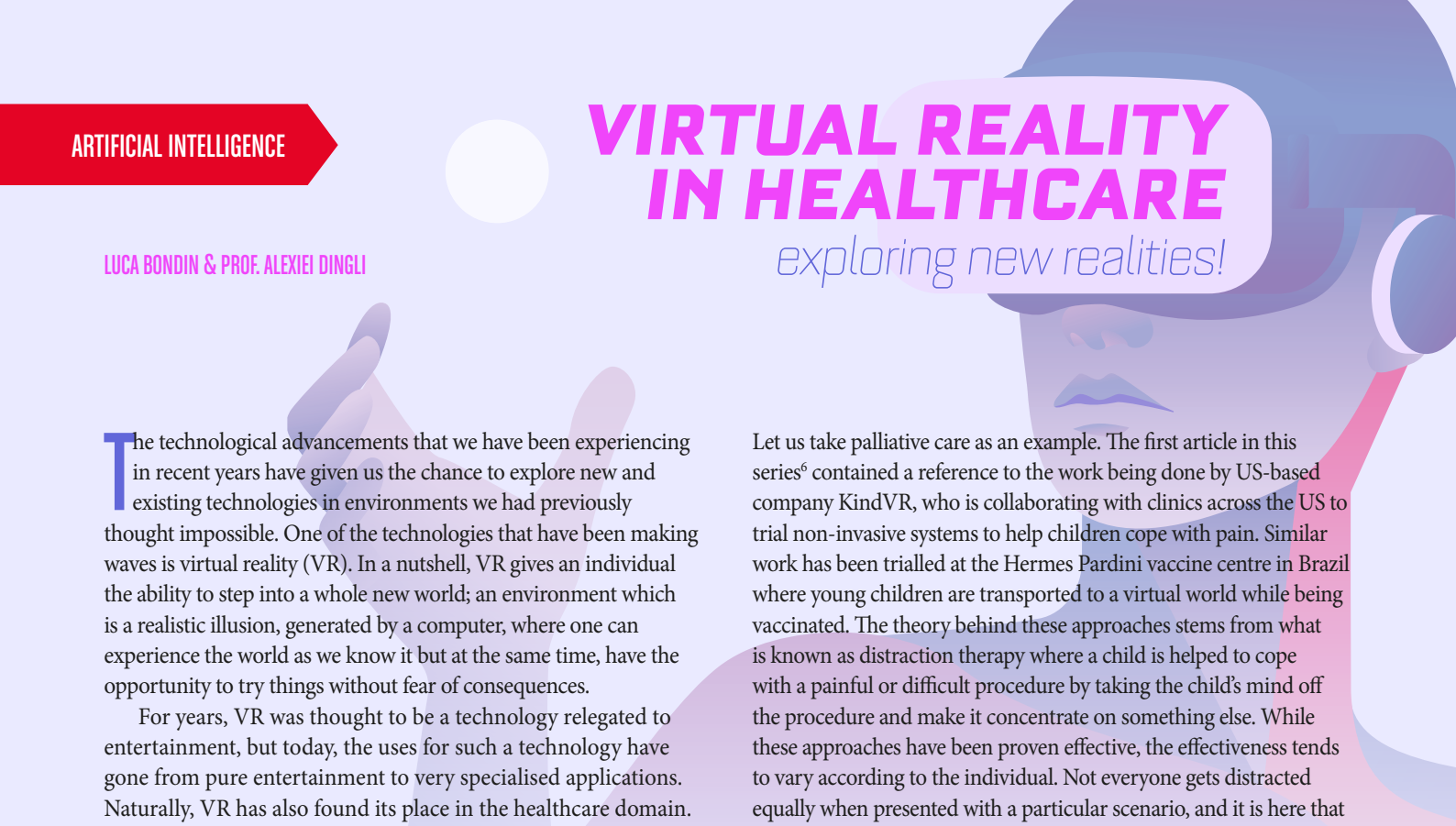
ISSUE GUIDE

TheSynapse

VIRTUAL REALITY IN HEALTHCARE

exploring new realities!

LUCA BONDIN & PROF. ALEXIEI DINGLI



The technological advancements that we have been experiencing in recent years have given us the chance to explore new and existing technologies in environments we had previously thought impossible. One of the technologies that have been making waves is virtual reality (VR). In a nutshell, VR gives an individual the ability to step into a whole new world; an environment which is a realistic illusion, generated by a computer, where one can experience the world as we know it but at the same time, have the opportunity to try things without fear of consequences.

For years, VR was thought to be a technology relegated to entertainment, but today, the uses for such a technology have gone from pure entertainment to very specialised applications. Naturally, VR has also found its place in the healthcare domain.

Perhaps the most evident application of VR in healthcare is its application as a teaching tool. In 1993, Richard M. Satava[1] presented his vision for a VR surgical simulator. Satava suggested that this VR simulator signalled the beginning of an era of computer simulation for surgery. Despite this early vision, it is only now that we are beginning to witness increased acceptance of such VR simulations. While the reasons for this resistance are numerous, the delay is attributed to two main reasons. First, the initial lack of robust scientific evidence to support the use of VR for skills training which gave rise to scepticism about the validity of the approach itself. Second, the lack of knowledge of how to effectively apply simulations to a surgical training program led to early discordant views about its effectiveness.[2] As the levels of acceptance for such approaches continued to grow, other researchers pioneered the use of VR in other areas of healthcare. Buchanan[3] details the use of VR in teaching dentists to carry out restorative dental procedures. Gardner et al.[4] explore the use of VR simulations for obstetrics and gynaecology training procedures. Other applications include orthopaedic surgery, mastoidectomy simulation, training and pre-treatment planning of interventional neuroradiology procedures, and training and assessment of laparoscopic skills. Beyond the confined "hospital" or "clinical" environments, VR environments have been used to train psychiatrists. One such application is currently being developed at the Department of Artificial Intelligence at the University of Malta as a teaching tool to simulate what happens inside the mind of a person with schizophrenia. Similarly, research has looked into teaching carers and educators how to help children on the autism disorder spectrum. Another study carried out by the same department[5] focused on helping professionals step into the daily lives of an autistic child.

The use of VR as a tool for teaching individuals is relatively intuitive. However, what really distinguishes VR as a technology is its adaptability and the manner in which it can easily be deployed in a wide variety of use cases outside the conventional applications.

Let us take palliative care as an example. The first article in this series[6] contained a reference to the work being done by US-based company KindVR, who is collaborating with clinics across the US to trial non-invasive systems to help children cope with pain. Similar work has been trialled at the Hermes Pardini vaccine centre in Brazil where young children are transported to a virtual world while being vaccinated. The theory behind these approaches stems from what is known as distraction therapy where a child is helped to cope with a painful or difficult procedure by taking the child's mind off the procedure and make it concentrate on something else. While these approaches have been proven effective, the effectiveness tends to vary according to the individual. Not everyone gets distracted equally when presented with a particular scenario, and it is here that Artificial Intelligence comes into play through a field of study known as affective computing. In a nutshell, affective computing aims to make computers intelligent enough to adapt their behaviour to how the user is feeling at that point in time. Through the application of affective computing we can, therefore, ensure that if, for example, a child is using a game similar to that developed by KindVR or the one being trialled at the Hermes Pardini centre, the game adapts itself to how the child is feeling making the child feel more comfortable and at ease. For example, if the child feels a burning sensation, then the game changes it's environment to one that justifies the burning sensation by introducing dragons and other such characters. As a consequence of this, the child is more immersed in the game, which results in a better and less painful intervention.

The opportunities that VR and Artificial Intelligence have given us in delivering a better overall experience to patients are truly immense. More important is the fact that we are now starting to appreciate them more and finding innovative ways on how to adopt and implement them in our everyday activities. If this trend does indeed continue, we can guarantee a much better overall experience for patients and care-givers in the upcoming years.

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Prepared: June 2018 Job No: MLT_GIB/AES/0001/18a

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DIAGNOSING COMMON TYPES OF TREMOR in TWO SHAKES

DR ADRIAN PACE

Tremor is defined as an involuntary, oscillatory, rhythmic movement of a body part produced by the alternating contractions of antagonistic pairs or muscles. It is the most common movement abnormality encountered and investigated in both primary care and neurology practice. Tremor is not a diagnosis in itself; rather it is symptomatic of an underlying disorder that should be identified and when possible treated. The diagnostic process ought to include a detailed medical history, a careful assessment of the characteristics of the tremor and a search for other neurological or physical signs. This process may present challenges, particularly in describing tremor phenomenology and linking it to the likely diagnosis. This article outlines briefly the main points to explore when evaluating a patient's tremor history, the key characteristics of tremor that should be examined for and the correct nomenclature for their description, followed by an overview of the common types of tremor encountered in clinical settings and pointers to their diagnosis.

EVALUATION OF THE PATIENT WITH TREMOR

MEDICAL HISTORY

- *Age at onset and progression since.*
- *Timing of the tremor* – does it mainly emerge at rest or on activity?
- *Past medical issues* – Up to 60% of patients with multiple sclerosis manifest tremor at some point in their disease, which may emerge and subside over time and have differing characteristics. Stroke survivors may also develop tremor, albeit far more acutely. Tremor-like movements may be seen in cases of kidney (action myoclonus) and liver (flapping asterixis) failure, but these movements are phenomenologically different. Anxiety is commonly associated with postural tremor, so if suspected one should enquire about relevant symptoms such as palpitations, chest pain and feelings of suffocation that have been already investigated unsuccessfully.
- *Family history of tremor* – essential tremor (ET) is considered genetic and hereditary though not all patients will report affected family members. Rarely, Wilson's disease will present initially with tremor.
- *Medication list and relation to onset of tremor* – drug-induced tremor is common, either as an iatrogenic adverse effect or due to toxicity from specific supra-therapeutic drug levels in serum.
- *Dietary habits* – regular excessive intake of strong coffee or energy drinks, as well as episodes of hypoglycaemia following skipped meals, may all cause tremor.
- *Alcohol intake and effect on tremor* – in people suffering from alcoholism, acute withdrawal can induce tremor, while chronic excessive alcohol intake causes tremor due to cerebellar degeneration. Conversely, small doses of alcohol will temporarily suppress ET.

CHARACTERISATION OF THE TREMOR

The assessment of a patient with tremor is based on two equally important actions - a careful observation of the characteristics of the tremor and the proper denotation of these observations. The former narrows down the list of differential causes and often may lead to establishing a diagnosis. The latter requires that physicians become familiar with and adopt the use of standardised nomenclature to avoid confusion and assist in the recording and conveying of information over time in patients' records.

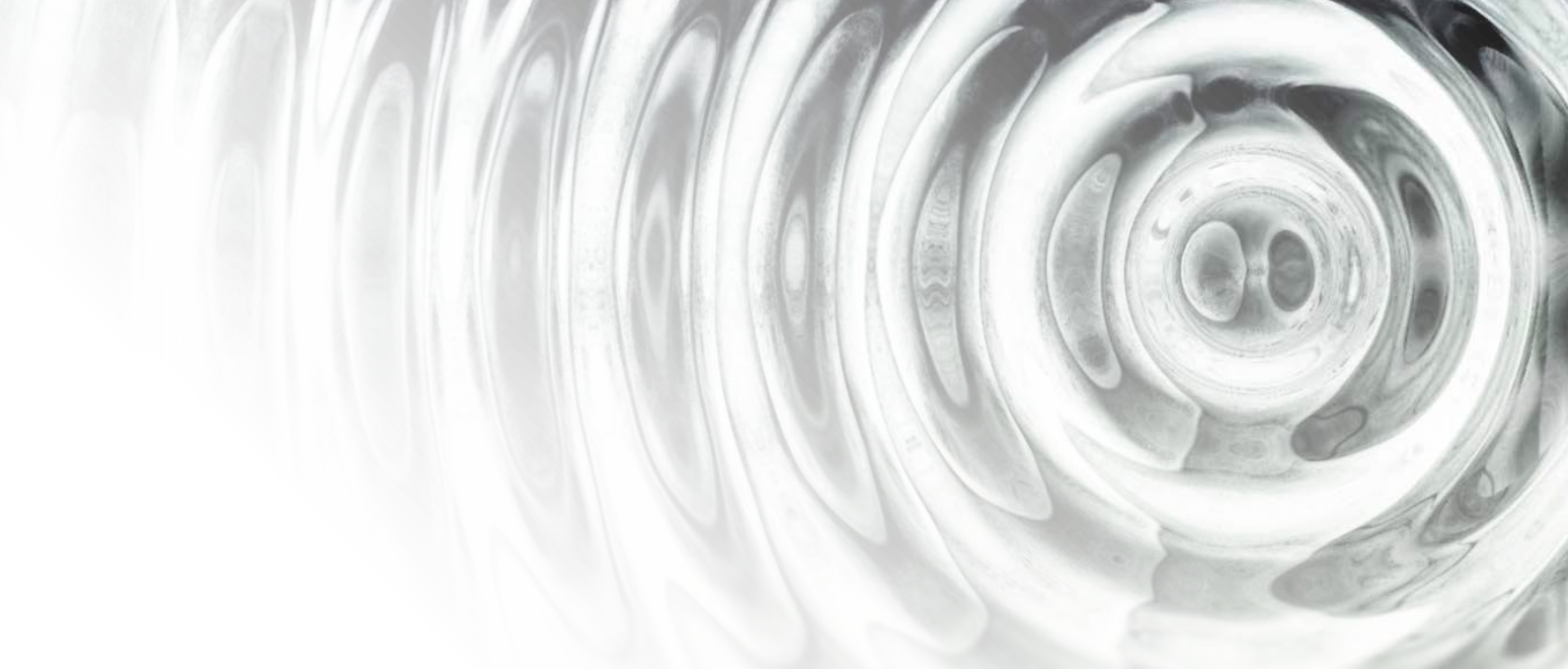
There are six primary characteristics of tremor that should be examined and recorded:

1. Anatomic distribution

- Note the affected body parts, which may include the head, tongue or palate, the upper or lower extremities, or the trunk. If the head is involved, note if the tremor is vertical (nodding / yes-yes tremor) or horizontal (shaking / no-no tremor).
- Look for vocal tremor while conversing with the patient and ask them to hum a note.

2. Frequency

The frequency of a tremor may not be measurable with the naked eye, but one may at least classify it as fast (>6Hz) or slow (<6Hz). Although there are differences in average tremor frequency among different types of tremors, the range of frequencies overlap considerably between disorders, so tremor



frequency is less helpful than other characteristics in reaching a diagnosis. However particularly slow tremors (≤4Hz) are only seen in Parkinson's disease (PD), cerebellar disorders, midbrain lesions or secondary to medication.

3. Position

The position of the affected body part when the tremor emerges or is most pronounced is the most important aspect of its evaluation. *Resting* tremor occurs when the body part is not voluntarily activated and is completely supported against gravity. *Action* tremor emerges during activity requiring voluntary muscle contraction and may be further specified into:

- *Postural tremor* which occurs when maintaining a voluntary posture against gravity as when holding the upper extremities in an outstretched position.
- *Isometric tremor* which occurs when muscles are contracted without appreciable movement (such as squeezing the examiner's fingers).
- *Non-target directed tremor* observed during non-goal oriented movements (such as flexion / extension of elbow or pronation / supination of the forearm).
- *Intention tremor* which occurs during target-directed movements, as in the finger-to-nose or heel-to-shin tests.
- *Task-specific tremor* appears or is exacerbated by performing specific tasks, such as writing, holding tools or playing a musical instrument.

4. Amplitude

Tremor is defined as either fine or coarse depending on the range of oscillatory movement in the affected body part(s). A general rule is to name the predominant tremor after the position in which the largest amplitude occurs (at rest / on posturing / during active movement).

5. Exacerbating or relieving factors

- Note if the amplitude is regular or variable and if it becomes more pronounced or lessens with distraction (ask the patient to say aloud the months of the year backwards with their eyes closed, or to flex and extend one elbow while examining the other hand).
- Ask if there is a temporary but significant reduction of tremor amplitude in response to alcohol, typical of ET (see below).

6. Associated symptoms and signs

- Eye movement abnormalities may suggest cerebellar disease or multiple sclerosis. Proptosis points to thyrotoxicosis (may also manifest tachycardia, a visible goitre and abnormal sweating).
- Kayser-Fleischer rings are specific for Wilson's disease.
- Torticollis, blepharospasm, orofacial twitching or spasmodic dysphonia (with effortful strained speech or a whispery voice) indicate dystonia.
- Extrapyramidal signs such as lack of facial expressivity, reduced blink rate, a monotonous voice, muscular rigidity or bradykinesia indicate idiopathic PD or parkinsonism.
- Gait may be parkinsonian (reduced length of stride, reduced or absent armswing, forward stoop, slow turning using several steps), cerebellar (broad based and ataxic) or spastic (suggesting multiple sclerosis).
- An otherwise completely normal neurological examination is both reassuring and usually suggestive of ET.

COMMON TYPES OF TREMOR PRESENTING TO GP CLINIC OR HOSPITAL OUTPATIENT SETTINGS

Exaggerated physiological tremor

Physiological tremor, a high frequency postural tremor of very small amplitude in the hands, is a normal phenomenon not associated with disease. This may not be visible to the naked eye but may be elicited more easily by placing a sheet of paper over an outstretched hand. The tremor may be magnified by anxiety, hypoglycaemia, exercise, caffeine or other stimulants. It may also become more pronounced in patients who withdraw from alcohol, use regular beta agonists, have thyrotoxicosis or Cushing syndrome. Reassurance, modification of health behaviours, or treatment of causative medical issues form the mainstay of its management, although tremor-suppressive agents or anxiolytics may sometimes have a role to play.

Essential tremor

Essential tremor (ET is the most common adult onset movement disorder. It is bilateral, usually but not invariably symmetrical, postural or kinetic, and involves the hands and forearms. It may also involve the neck (causing head titubation) and / or voice but rarely affects the legs. It tends to emerge gradually as a high frequency (>5Hz) slight tremor that increases slowly in amplitude over time, impacting progressively on activities of daily living such as eating with cutlery, holding beverages or bringing them to the lips without spilling, and activities requiring finger dexterity such as fastening buttons, threading a needle or writing. ET appears in people within the age bracket where idiopathic PD starts increasing in prevalence. An important distinguishing feature is that PD tremor may occur on posturing but appears after sustaining a fixed posture for several seconds, while ET does not manifest a delay its onset on posturing. A further distinguishing feature is a noticeable albeit temporary, reduction of tremor amplitude in response to alcohol. A positive family history is reported in about 50% of patients affected by ET.

Parkinsonian tremor

The typical PD tremor is a pure resting tremor with low frequency (4–6 Hz). Tremor amplitude varies both across and within patients, tending to become less notable over time as bradykinesia concomitantly becomes more pronounced. The correct diagnosis may be made very easily if the patient also manifests other cardinal signs of PD, namely bradykinesia or extrapyramidal rigidity. However tremor may be the sole presenting feature of PD, in which case telling it apart from ET may be challenging. In these cases, the following pointers may prove helpful:

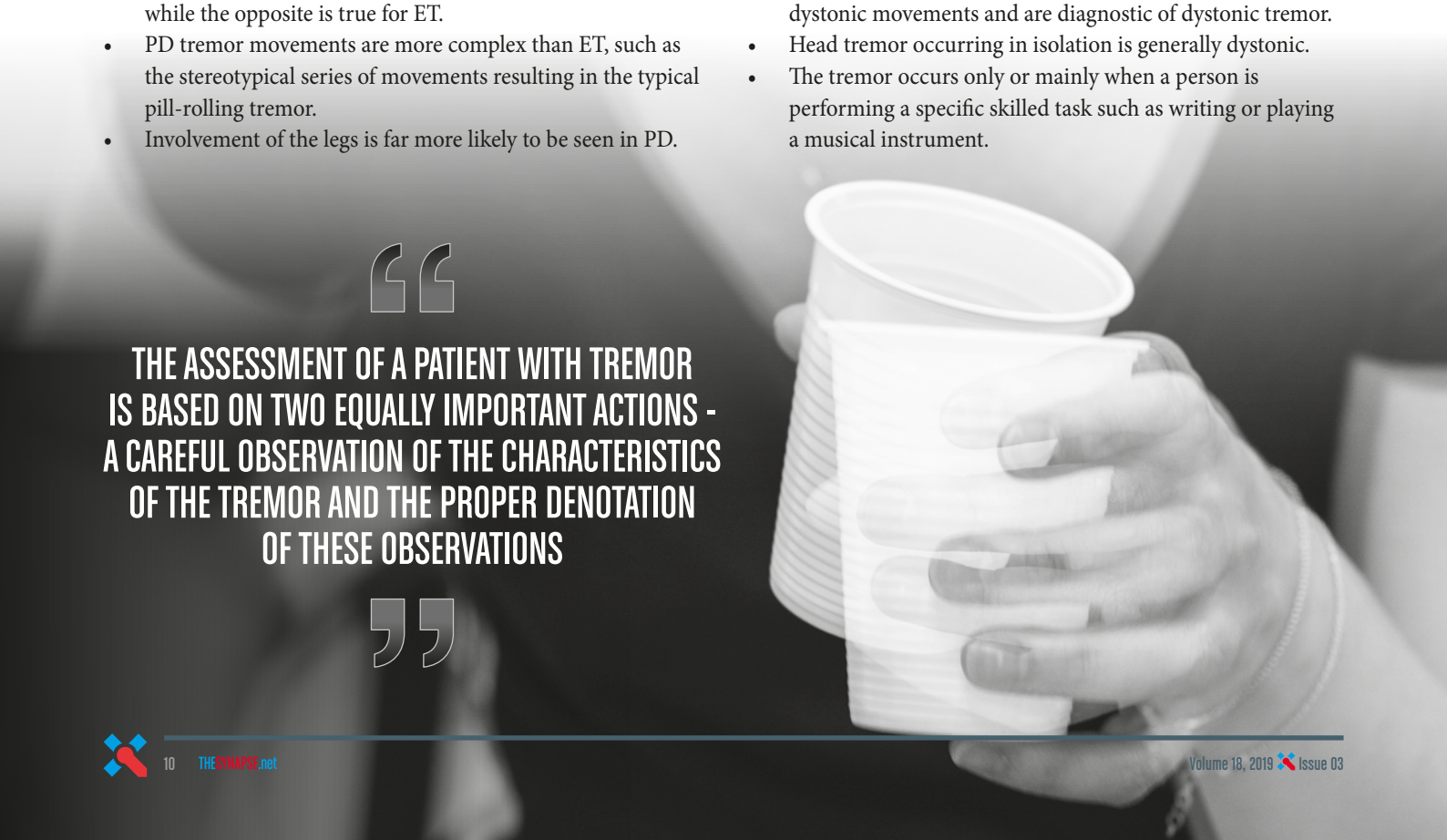
- PD tremor is much more likely to be unilateral or asymmetrical than ET.
- PD tremor at rest is more pronounced than on activity, while the opposite is true for ET.
- PD tremor movements are more complex than ET, such as the stereotypical series of movements resulting in the typical pill-rolling tremor.
- Involvement of the legs is far more likely to be seen in PD.
- When present, postural tremor in patients with PD will appear after a latent period of several seconds. This is referred to as a re-emergent tremor.
- Observing gait may confirm the presence of PD tremor as the arms are relaxed by the patient's sides, often with reduction in armswing, while patients with ET do not generally have tremor while walking.

When the diagnosis remains unclear, a trial of antiparkinsonian medications may help, as ET should not respond. Do keep in mind that tremor in PD is often more difficult to alleviate than bradykinesia and rigidity, and tends to respond less well to dopaminergic therapy or may not improve with medication at all. Some patients need to be followed up over time until emergent hypokinetic symptoms and signs confirm the diagnosis of PD.

Dystonic tremor

Dystonic tremor (DT) is a focal tremor in an individual with dystonia. The tremor is mainly postural or kinetic, and may occur in the body part affected by dystonia, or in different areas. The diagnosis of DT is straightforward when accompanied by overt focal or segmental dystonia, but may be misdiagnosed when tremor is the predominant complaint, and accompanying symptoms such as mild blepharospasm or torticollis are missed or their significance overlooked. However DT should be distinguishable in that:

- Careful observation will reveal tremor of irregular and variable frequency and amplitude.
- The affected body part tends to move more in a particular direction.
- The patient may report having a sensory trick to control the tremor. These '*gestes antagonistes*' are voluntary maneuvers (such as simply touching or putting light pressure on the affected area) that temporarily reduce the severity of dystonic movements and are diagnostic of dystonic tremor.
- Head tremor occurring in isolation is generally dystonic.
- The tremor occurs only or mainly when a person is performing a specific skilled task such as writing or playing a musical instrument.



> THE ASSESSMENT OF A PATIENT WITH TREMOR IS BASED ON TWO EQUALLY IMPORTANT ACTIONS - A CAREFUL OBSERVATION OF THE CHARACTERISTICS OF THE TREMOR AND THE PROPER DENOTATION OF THESE OBSERVATIONS

Cerebellar tremor

This is primarily an intention tremor that may also manifest on posture. It is of slow frequency (<5Hz) and its amplitude typically increases as the body part undergoing movement approaches the target, as in the finger-to-nose test. Tremor distribution primarily depends on aetiology. Focal structural pathologies due to neoplastic growths, and vascular or inflammatory insults to the cerebellum may present with unilateral tremor, while genetic or toxic disorders resulting in cerebellar degeneration, such as chronic alcoholism, long-term exposure to certain medications or spinocerebellar ataxias are likely to cause bilateral tremor. Other relevant clinical signs such as dysarthria, nystagmus and ataxia of gait, trunk or limbs, usually accompany the tremor and point to the correct diagnosis, with investigations mainly helping to identify the underpinning cause.

Drug-induced tremor

Medication should always be considered as a potential cause for a patient's tremor, although iatrogenic causes of tremor probably remain under-recognised. Identifying drugs that may cause or exacerbate tremor can expedite diagnosis, avoid unnecessary tests and ensure the right approach to management (discontinuing the tremor-inducing drugs rather than prescribing tremor-suppressive agents). There may be a significant time-lapse (months to several years) between starting the offending drug and onset of tremor. Likewise, once the drug is identified and removed, it can often take time for the tremor to improve. An exhaustive list of drugs causing tremor is beyond the scope of this article, but a comprehensive review of the subject has been authored by Morgan and Sethi (See Further Reading).

Diagnosis of a drug-induced tremor may be challenging for three reasons. Firstly, a large number of different medications are recognised as tremorogenic, and it would not be unusual to encounter elderly patients with tremor on a long list of medications that includes two or more of these. Secondly, stopping suspected drugs may be impossible or potentially unsafe if no equally effective alternative is available. Thirdly, drug-induced tremor may demonstrate the entire spectrum of clinical features of tremor, depending on the offending agent. Thus stimulants will cause an exaggerated physiological postural tremor, dopamine blocking agents will result in a Parkinsonian resting tremor, and chronic alcoholism or long-term valproate therapy will cause a cerebellar intention tremor.

Psychogenic tremor

Psychogenic tremor should be considered in the differential diagnosis of any patient with tremor.

Differentiating psychogenic tremor from an organic tremor can be very challenging, and misdiagnosis is not uncommon. There are however several clues that may point to a psychogenic cause:

- The tremor is often difficult to fit into a recognisable pattern, generally starts suddenly rather than gradually, and often varies in amplitude and frequency.
- Tremor may transiently disappear or change in its frequency with distraction maneuvers, such as asking the patient to perform voluntary movements in the contralateral limb such as alternate finger tapping or foot tapping. Suggestion is another method whereby a vibrating tuning fork is applied to the patient's forehead after giving the impression that this may stop the tremor – which typically stops or diminishes temporarily.
- A past history of somatisation (unexplained chest pain, breathlessness, fatigue, gastrointestinal symptoms or sensory disturbances despite multiple investigations) is often encountered when enquired about. Some patients may develop tremor during a grieving period.
- The diagnosis of psychogenic tremor, when suspected, should be confirmed by a neurologist, both due to the difficulty in reaching the diagnosis as well as the resistance by some patients to accept a non-organic reason for their symptoms.

Neuropathic tremor

Tremor may occur in patients suffering from peripheral neuropathies, in particular demyelinating neuropathies. An association should be considered in patients previously diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP), hereditary neuropathies including Charcot-Marie-Tooth disease or monoclonal gammopathy. The tremor is generally postural and kinetic in nature, predominantly distal in location with atypical jerky-like and pseudoathetotic or abduction-adduction pattern of movements in the fingers. It usually affects the upper limbs in a symmetric or asymmetric fashion and has a slow to moderate frequency (3-6Hz). When it is the first presenting symptom of neuropathy, examination will yield hallmarks of a generalised peripheral neuropathy including absent or subdued reflexes, weakness, impaired sensation, ataxia and gait disturbance.

Treatment of the underlying neuropathy (when possible) may suppress or resolve the tremor.

Orthostatic tremor

Orthostatic tremor is a tremor disorder of the lower extremities which is uncommon but worth highlighting due to its specific clinical presentation. Sufferers do not report tremor but rather a feeling of unsteadiness when attempting to stand still for longer than a few seconds. This feeling disappears on walking or on sitting down. Diagnosis is confirmed using surface electromyography which demonstrates a very high frequency (12–18 Hz) tremor in affected muscles. The muscle contractions can be auscultated through a stethoscope applied to the thigh or calf, as these generate a rapid staccato sound has been compared with that of a helicopter rotor ('helicopter sign').

FURTHER READING

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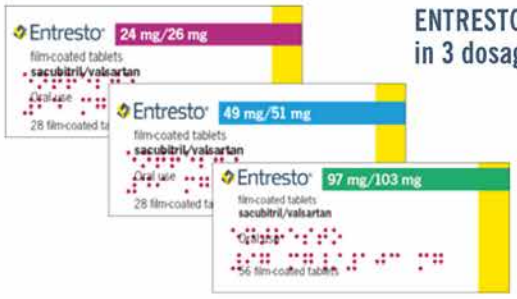

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Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. Warnings/ Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. Undesirable effects: Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. Legal classification: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. Please refer to the 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 21222872. 2018-MT-ENT-30-APR-2018

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DO ALL PROSTATE CANCERS NEED ACTIVE TREATMENT?

IS THERE A ROLE FOR INTEGRATIVE MEDICINE?

SHORT ACCOUNTS OF INTERESTING CASES, SOME MEDICAL DISASTERS, INVOLVING PATHOLOGY AND CLINICAL PRACTICE, FROM THE RECOLLECTION OF PROF. ALBERT CILIA-VINCENTI.

Exactly ten years ago, a friend of mine asked me to discuss his recent prostate cancer diagnosis. He was 75 years old, tall and slim, in overall good health, but had just had received a diagnosis of a Gleason score 7 (3+4) prostate carcinoma on his transurethral resection prostate chips. The tumour had been found incidentally during the transurethral resection of the prostate (TURP), as part of procedures to deal with outflow obstruction, bladder stones and unilateral hydronephrosis. Pre-op total PSA was 6.47.

Before retiring in Malta, this patient had been a senior civil servant in London and had also a longstanding interest in integrative medicine. He asked me to review his histological slides, particularly with a view to gauge whether there was any chance he could avoid the radiotherapy and hormone treatment that had been recommended.

I reviewed the histology and noted that a quarter to a third of the chips were occupied by a uniform very well differentiated prostatic adenocarcinoma most resembling the so-called "foamy gland" type; no other morphological pattern was present. In the pre-Gleason era this tumour would have been given a grade 1, out of a maximum of 3. With the Gleason system his TURP material would be scored (1+1) 2. The Gleason system does not permit scores of less than 6 on needle biopsies because of the high probability of non-sampled higher grade tumour. It is also possible that TURP material does not include more aggressive peripherally situated tumour.

I discussed my findings with the patient, namely that his pathology suggested an indolent progression which might ideally be suited to "watchful waiting" / active surveillance". There was evidence this do-nothing approach for such a low grade tumour offered no less survival longevity than radical prostatectomy or radiotherapy.[1] Professor Dean Ornish, integrative cardiologist, urologist Dr Peter Carroll (both of California) and the late Dr Peter Fair (urologist, Memorial Sloan-Kettering Cancer Center, New York) had shown in a randomised controlled trial that their lifestyle medicine programme (more plant and less animal-derived food, regular exercise and stress management) may slow, stop or even reverse the progression of early-stage, low grade prostate cancer, without drugs or surgery.[2]

Other researchers[3] found that men diagnosed with prostate cancer who ate a diet high in red and processed meat, high-fat dairy and refined grains had a higher risk of both prostate cancer-related mortality and overall mortality compared with those who ate a whole-foods plant-based diet. They examined health and diet data from almost 1,000 men participating in the Physicians' Health Study who were diagnosed with prostate cancer and followed them up for an average of 14 years. Men who ate mostly a Western diet had a 250% higher risk of prostate cancer-related death, and a 67% increased risk of death from any cause. In contrast, men who ate mostly a whole-foods plant-based diet had a 36% lower risk of death from all causes.[3]

The patient discussed my lower scoring of the tumour and my suggested active surveillance approach with his urologist who agreed that this was a possible approach but warned that the patient would have to accept full responsibility for that decision. This patient decided to follow Dean Ornish's integrative medicine approach, combined with active surveillance, and to avoid radiotherapy or any pharmacological intervention. It requires a disciplined personality, particularly to modify one's diet, which this patient did have.

For what it is worth, he also followed my advice to take daily fish oil and other food supplements which, besides multivitamins (including vitamin D3), contain lycopene and saw palmetto which may dampen the effect of oestrone and dihydrotestosterone on prostate cells, and also Reishi mushroom extract which might improve anti-tumour immunity. Ten years later, his total PSA never exceeded 2.42, his June 2019 level was 1.38, and he is a reasonably fit 85-year old on no pharmaceutical drugs. Had he submitted himself to radiotherapy, this 10-year success story would have been falsely attributed to that treatment.

This successful outcome also depended on the second opinion's lower grading of the tumour. The Gleason system is claimed to have improved treatment decisions, but interpreting and applying it is far from straight forward. In fact, there tends to be good grading agreement between urological pathologists but less consensus among general pathologists.[4] This case illustrates the problem of possible tumour grading disagreement and the consequences for management choices. Furthermore, one wonders whether this might be the only Maltese case of a 10-year documented active surveillance follow-up for prostate cancer.

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TRADE NAME: Wellbutrin XR modified release tablets. **ACTIVE INGREDIENT:** Bupropion Hydrochloride, 150mg/300mg. **PHARMACEUTICAL FORM:** Modified release tablet. **INDICATIONS:** Treatment of major depressive episodes. POSOLOGY: Should be swallowed whole with or without food. Tablets should not be cut, crushed or chewed as this may lead to increased risk of adverse effects including seizures. *Adults:* Recommended starting dose is 150 mg, once daily. If no improvement is seen after 4 weeks, dose may be increased to 300 mg, once daily. There should be interval of at least 24 hours between successive doses. Patients should be treated for a sufficient period of at least 6 months. Full antidepressant effect may not be evident until after several weeks of treatment. Insomnia may be reduced by avoiding dosing at bed time. *Children and Adolescents (less than 18 years of age):* not indicated. *Discontinuing therapy:* a tapering off period may be considered. *Refer to full SPC for full Posology details.* **CONTRAINDICATIONS:** Hypersensitivity to Bupropion or any of the excipients; co-administration with other medicinal products containing Bupropion (incidence of seizures is dose-dependent); current seizure disorder or history of seizures; known CNS tumour; patients undergoing withdrawal from alcohol or any medicinal product known to be associated with risk of seizures on withdrawal; severe hepatic cirrhosis; current or previous diagnosis of bulimia or anorexia nervosa; concomitant use with MAOI's. **PRECAUTIONS:** *Seizures:* Recommended dose should not be exceeded; Caution in patients with predisposing risk factors for seizures such as concomitant administration of medicinal products known to lower the seizure threshold (e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones, sedating antihistamines), alcohol abuse, history of head trauma, diabetes treated with hypoglycaemics or insulin, use of stimulants or anorectic products; should be discontinued in patients who experience a seizure during treatment; *Interactions:* Bupropion inhibits metabolism by cytochrome P450 2D6; Caution is advised when medicinal products metabolised by P450 2D6 are administered concurrently; Use of Wellbutrin XR, which is an inhibitor of CYP2D6, should whenever possible be avoided during tamoxifen treatment; *Neuropsychiatry: Suicide/suicidal thoughts or clinical worsening:* Careful monitoring should be carried out during first weeks of treatment, during dose changes and in patients who have history of suicide-related events prior to treatment; close supervision should accompany drug therapy in particular those at high risk especially in early treatment and following dose changes; Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medicinal product, in patients who experience the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms; increased risk of suicidal behaviour with antidepressants in patients less than 25 years old compared to placebo. *Neuropsychiatric symptoms including mania and bipolar disorder:* Neuropsychiatric symptoms have been reported. In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. Caution in patients receiving ECT therapy concomitantly. *Hypersensitivity:* should be discontinued promptly if patients experience hypersensitivity reactions during treatment; *Cardiovascular Disease:* caution in patients with cardiovascular disease due to limited clinical experience. Bupropion was generally well tolerated in studies for smoking cessation in patients with ischaemic cardiovascular disease. Monitor blood pressure especially in patients with pre-existing hypertension; consider discontinuation if a clinically significant increase in blood pressure is observed; Concomitant use with a nicotine transdermal system may result in elevations of blood pressure. *Other:* Treatment with antidepressants is associated with increased risk of suicidal thinking and behaviour in children & adolescents with major depressive disorder and other psychiatric disorders. Use with caution in patients with mild to moderate hepatic impairment. Patients with renal impairment should be closely monitored. Older people: Greater sensitivity in some older individuals cannot be ruled out. Bupropion interferes with the assay used in some rapid urine drug screens which can result in false positive readings. 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Job No: PM-MT-BPR-ADVR-190001
Prepared: April 2019

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* MDD: Major Depressive Disorder; SSRI: selective serotonin reuptake inhibitor
^ SSRIs: sertraline, citalopram, escitalopram, paroxetine and fluoxetine
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DR MICHELLE MUSCAT

A VERY VILE KROKODIL

A homemade injectable desomorphine concoction goes by the street name krokodil,[1] alternatively dubbed 'Russian magic'. Desomorphine is an opiate derivative. Krokodil has also been referred to as 'the drug that eats junkies'.[2]

This can be made for recreational purposes from a cocktail including ingredients obtained over the counter, notably codeine and other additives such as iodine, and red phosphorus from match striking surfaces. Given the illicit nature of the brews, it may have varied constituents and complexities in chemical composition with both different metabolites and contaminants.[3]

Drug addicts generally switch from heroin to krokodil due to financial reasons given that it is cheaper.[4] In 2017 a study by Soares et al detected 54 morphinans which may potentially play a role in krokodil's psychotropic action.[5] Another analysis deemed that desomorphine is present as the major compound together with two other morphinans.[6] It is best known as originating in Russia.[7] It may cause skin necrosis[8-10] as part of krokodil's 'nasty bite' with the appearance similar to scaly discoloured 'crocodile skin'.[11] Osteonecrosis of the maxilla is common with krokodil.[12-14] Fatal endomyocarditis has also been reported.[15]

Other effects include gangrene, ulceration and infection. There is a high mortality with its use.[16-17] Although krokodil is generally injected intravenously, in 2016 Baquero et al reported a case where krokodil had been ingested orally.[18] In recent years, experiments on rat models were carried out showing altered biochemistry, in keeping with its toxicity and probable oxidative stress which is caused. Biochemical findings showed changes in creatinine kinase and uric acid, as well as glutathione levels.[19] Patterns of internet searches on the topic of this drug have also been studied. Infoveillance studies can be seen as novel approaches for the monitoring of illicit drug use.[20-21]

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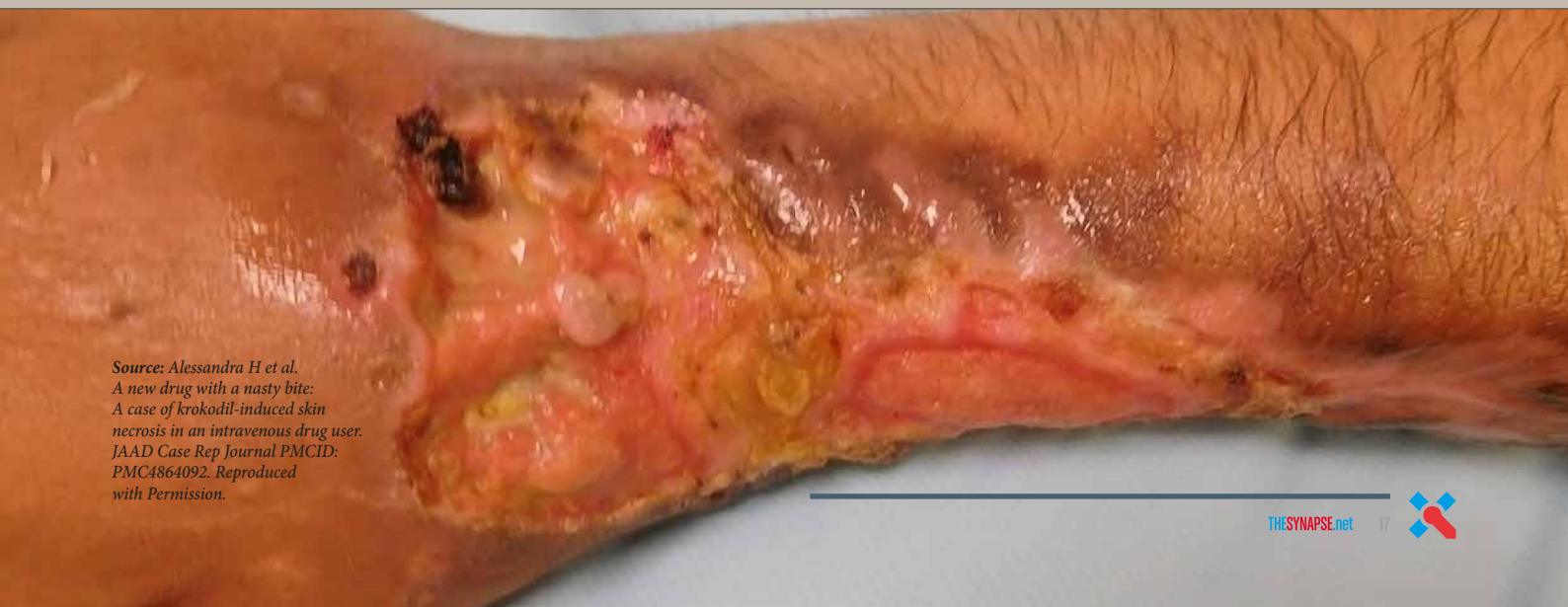

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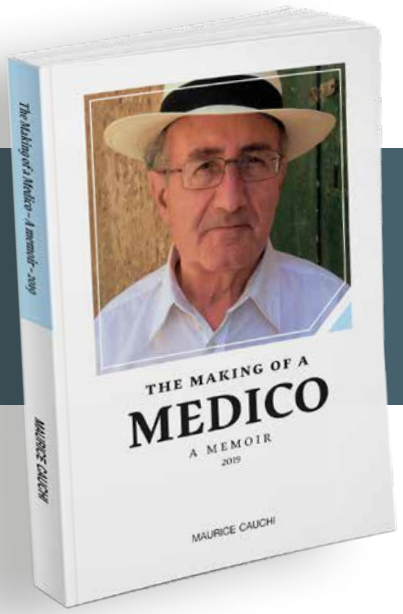
Gozitan A MEDIC DOWN UNDER



Dr Ian Ellul chats with PROF. MAURICE CAUCHI – retired Professor of Pathology based in Australia - over a cup of tea at his residence in Marsalforn. Prof. Cauchi is member of the Order of Australia and has been awarded the Medal for Services to the Republic of Malta.

YOU WERE BORN IN GHARB, GOZO IN 1936. WHAT ARE YOUR CHILDHOOD MEMORIES?

We had the most idyllic life ... playing with friends in the street which served as football ground and spending entire days on end at the beach. On the other hand I also remember clearly being carried on shoulders in the middle of the night to the war shelter; I was only four years when WW II broke out.

I also cannot forget the village festa which was awe-inspiring. Remember that in those days there was no electricity. Imagine the streets in Gharb back then - lit with kerosene lamps which were placed at regular intervals – suddenly being illuminated, though momentarily, by the red, orange, blue and green fireworks... this experience is beyond comprehension for today's children.

I also recall the harvesting, winnowing and threshing of wheat during summer. Gharb used to produce a lot of wheat. Entire families would help in the harvesting of wheat, reaping and then placing the wheat in large sheaves. These were then left to dry out and in sultry weather days (riħ eħtrieq), farmers would take these sheaves to be separated from the chaff (ħuxlief). The threshing was done on a large floor (il-qiegħa). Donkeys or mules would be harnessed next to each other and these would go in circles, crushing the wheat and separating the grain from the husk. Farmers would then use a pitch-fork to throw the grain in the air. The wind would blow away the lighter chaff, whilst the grains, being heavier, would fall back down on the ground. A sieve would then be used to sift the grain.

CAN YOU TELL ME MORE ABOUT YOUR FAMILY IN GHARB?

I was one of five siblings. The late Bishop Nikol Cauchi was my brother. I also have another one who is priest, Mgr Achilles Cauchi. Then there are two sisters. My mother was a house-wife. Our father, who was a sacristan, died relatively young at 56 years of age. He required a dialysis machine since he suffered from renal failure. This was unavailable in Malta at the time. I recall that a certain Dr Tua used to perform peritoneal dialysis with saline. My far as my memory stretches, I always remember him deteriorating with time. He literally died in my hands…

AFTER GRADUATING IN 1961 YOU WENT TO THE UK AND READ FOR A MASTERS AT MIDDLESEX HOSPITAL AND THEN FURTHERED YOUR STUDIES AT THE ROYAL MARSDEN HOSPITAL WHERE YOU ATTAINED A PHD IN CANCER RESEARCH. A YEAR AFTER YOU FINISHED YOUR STUDIES, IN 1968, YOU RETURNED TO MALTA. I UNDERSTAND THAT BACK THEN, THE UK WAS THE COVETED DESTINATION OF MEDICAL GRADUATES. WHY DID YOU LEAVE THE UK?

Well, I returned to Malta to take a post of lecturer in Pathology at the UoM and settle here. At the Pathology Department I managed to find a new foetal haemoglobin variant which I named Hameoglobin F Malta. However, regretfully after six months I came at loggerheads with the Head of Pathology Department since he did not want me to continue my research. This was a watershed moment in my career because I desperately needed to finalise my studies. At this stage Prof. Arthur P Camilleri and Dr Anthony Cuschieri stepped in and offered me a post within the Obstetrics department for those critical months which were needed to finish my work. I will always be indebted to them for this honorous deed.

BARELY A YEAR AFTER, IN 1969, YOU PROCEEDED TO MELBOURNE WHERE YOU TOOK A JOB AS SENIOR LECTURER AT MONASH UNIVERSITY. YOU NEVER LOOKED BACK UNTIL 1992. WHY OPT FOR AUSTRALIA?

The decision was between Australia, Canada and the UK. I did what I had to do in the UK which I must admit, did not offer attractive salaries back then for my grade. I chose Australia since the salary was better than Canada, and it was also warmer.

YOU RETURNED TO YOUR ROOTS IN 1992, THIS TIME AS PROFESSOR OF PATHOLOGY AT THE UOM AND DIRECTOR OF PATHOLOGY, ST LUKE'S HOSPITAL. I CAN UNDERSTAND THIS, BUT IN 2003 YOU RETURNED YET AGAIN TO AUSTRALIA. WAS NOSTALGIA THAT BAD?

I used to commutate between Malta and Australia every two years or so, but in 1992 I returned to Malta and stayed there

for 11 years. My decision to move back to Australia in 2003 stemmed from various reasons, including nostalgia since many of my friends were there. However, the main reason was that my daughter gave birth to twins and my wife wanted to be near her. I was retired by that time so there was nothing which held me back.

IN AUSTRALIA YOU WENT TO GREAT LENGTHS TO CHAMPION ALL MATTERS RELATING TO MIGRATION AND ETHNICITY. IN KEEPING WITH THIS YOU HAVE ADVOCATED THESE ISSUES THROUGH THE MALTESE COMMUNITY COUNCIL OF VICTORIA AND MALTA VIRTUAL MIGRATION MUSEUM, TO NAME A FEW. WHAT MADE YOU DO ALL THIS?

When I first went to Australia I immediately realised that the Maltese migrants were in dire need of a structure to safeguard their cultural roots. However, due to my work commitments, it was not until the 80's that I actively started pursuing the matter through the Maltese Community Council of Victoria with a view to elevate the status of the Maltese living in Australia. Remember that almost all Maltese migrants were blue-collar workers, which reflected the average Maltese back in Malta. Indeed, I had conducted a study which found that only 1-2% of Maltese migrants had a higher degree, similar to Malta. However, the lack of education was more than compensated by their technical expertise since many migrants were ex-Dockyard workers. Almost all built their own houses. In fact, Maltese migrants have one of the highest home ownerships in Australia. I would also like to mention that also, in Malta, we had hereditary education i.e. if the father is a lawyer, most probably one or more of his children would follow suit. This was not the case for Maltese migrants in Australia.

DO YOU REMEMBER MALTESE COLLEAGUES WHO WERE MIGRANTS LIKE YOU?

Back in the 80's, many Maltese doctors either went to the UK, Dubai or Australia. In Australia I met Dr Louis Grech [forensic pathologist], Dr Herbert Lenicker [Medical Director, Williamstown Hospital], Dr Roger Parnis [surgeon] and Prof. Peter Castaldi, a professor of Medicine, born in Australia of a Maltese father. Then there were Dr Franco Bonnici [gynaecologist], Prof. Stephen Gatt [anaesthetist], Dr Francis Parnis [medical oncologist], Dr Paul Psaila-Savona [Executive director Public Health] and Dr Carmel Sammut [general practitioner].

I SEE YOU HAVE A PIANO AND CELLO. YOU LOVE CLASSICAL MUSIC?

Yes, indeed. It all started when I was young; my uncle had a harmonium and my cousin helped me learn the piano. Mostly autodidactic, I can play Mozart and some Beethoven. However, in view of problems in my right hand, some three years ago I started to take cello lessons, which is ideal since I make use of my left hand. I have now reached grade 7.

HOW DID YOU SEE GOZO CHANGE IN THESE LAST DECADES?

I remember when we had one ferry as means of locomotion between the islands, then the services of a helicopter was added (and removed) and now we have four ferries. One must appreciate the fact that to go from Marsalforn to example, Mater Dei hospital, one needs at least half a day. I have mixed feelings on the proposed tunnel. However I must add that an efficient transport system underpins the smooth running of Gozitan businesses, amongst other things.

Gozo has become very noisy, and this stems from the over-development which we are experiencing. Buildings which were once four floors are now being developed into five floors (whilst the permit for the sixth floor is being nailed to the facade).

YOU LIKE WRITING, ESPECIALLY HISTORY RELATING TO MIGRATION, AND EVEN POETRY. AMONGST YOUR PUBLICATIONS, IN 2018 YOU PENNED *HEALTH AND SOCIETY: PERSONAL AND SOCIAL DETERMINANTS OF HEALTH WITH SPECIAL REFERENCE TO THE MALTESE ISLANDS*. THIS BOOK DISCUSSED CHALLENGES RELATING TO THE CHANGING PATTERNS OF HEALTH AS THEY AFFECT TODAY'S SOCIETY... ENVIRONMENTAL FACTORS, PARTICULARLY POLLUTION AND STRESS. WHAT MOTIVATED YOU TO WRITE THIS BOOK?

The book was penned as an education interphase between medicine and the general public. This is not something new; 20 years ago I had penned another book *Ix-Xjenza u s-Socjeta'*. An article written along the same lines, 'Doctors as Intellectuals', has also been published by *The Synapse Journal* some time ago.

YOU ARE WRITING ANOTHER BOOK, RIGHT?

Yes, the book goes by the name *'The Making of a Medico - a Memoir'*. It is basically a narrative of my life ... how it all began, my childhood, education, family, career… I will also discuss the bouts of depression suffered during my University life, stemming from the isolation which I faced back then. It was very challenging for Gozitan students to study in Malta. Remember that in those days there was no mobile, Facebook, or the like. You were alone.

The book also delves on the extensive research which I conducted on the issues relating to Maltese migrants in Australia. I managed to research 1st, 2nd and even 3rd generation migrants. I can staunchly say that the main challenge is the loss of culture, including language.

I refer you to my repository of online publications, https://mauricecauchi.wordpress.com/

FROM WHERE CAN ONE BUY THE BOOK?

The book, priced at Euro 15, can be bought from leading booksellers or directly from BDL (Book Distributors Ltd). The ISBN is 978-9957-1-556-3.

FROM YOUR EXPERIENCE AS PATHOLOGIST, WHICH IS THE MOST IMPORTANT RISK FACTOR FOR CANCER?

Being overweight, since the hormones associated with over-eating can be linked to colon and breast cancer, amongst other things.

I READ THE SYNAPSE BECAUSE...

It is a means of accessing research which is being conducted in Malta. I also appreciate the interviews. Keep up the good work!

BI-RADS GUIDE TO THE NON-SPECIALIST

UNDERSTANDING THE BREAST SPECIALIST'S JARGON

DR PIERRE VASSALLO

According to the American Cancer Society, approximately one in eight women will develop breast cancer during their lifetime. This is why breast cancer screening has become so important and why it is being given so much attention by healthcare planners. A standardised and evidence-based protocol for breast cancer screening and breast cancer management is needed to optimise treatment outcomes. This has been the driving force behind the development of BI-RADS, which stands for *Breast Imaging Reporting and Data System.*

In the past, the medical jargon used for describing imaging findings on mammograms, was highly non-standardised and was influenced by personal preference. This often led to miscommunication and sometimes even mismanagement due to misinterpretation of communicated results.

These factors led to efforts that started in the late 1980s aimed at standardising mammographic terminology and reporting. In 1993, the first edition of the BI-RADS lexicon was issued by the American College of Radiology.

The advantages of using BI-RADS are as follows:

- It allows standardised, rational and structured analysis of the breast
- Reporting nomenclature is standardised, which avoids confusion
- It facilitates communication between breast specialists and clinical staff involved in the management of breast cancer patients to enhance management
- It facilitates monitoring of treatment outcomes
- It facilitates education of breast care specialists.[1]

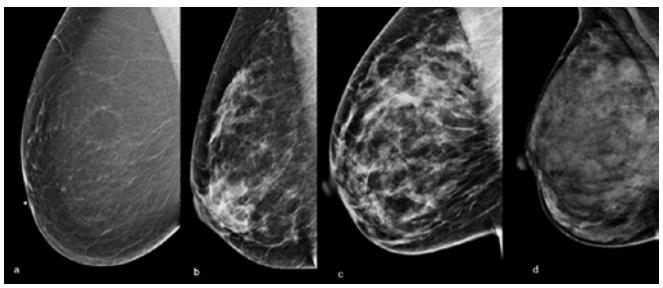


Fig 1. Breast Type as seen on mammography: **a.** predominantly fatty breast, **b.** a breast containing scattered fibroglandular elements, **c.** a heterogeneously dense breast, and **d.** a very dense breast.

The BI-RADS mammography lexicon is presently in its 5th edition and it is regularly revised based on experience and learning.[2] Meanwhile, BI-RADS lexicons have also been developed from Breast Ultrasound and for Breast MRI, both now in their 2nd edition.

While BI-RADS is mainly used by breast care specialists, a basic understanding of its significance is also important for patients and their care-givers. It allows them to understand their breast imaging results and helps them participate in their treatment.

A standard mammography report should follow a standard structure:

1. It should start with a statement indicating why the mammogram is being performed (screening or to follow-up a previously detected lesion) and the date/s of the previous exam/s to which the present one is being compared.
2. The next statement should indicate the breast type, which is classified based on the balance between fatty and fibro-glandular components into four types: predominantly fatty, patchy fibroglandular elements, heterogeneously dense breast and very dense breast (Figure 1). Breasts are considered very dense if they contain a lot of fibro-glandular tissue (>75%) and little fat (Type 4), while they are classified as fatty if they contain mostly (> 75%) fat (Type 1). Breast density is important for several reasons. Dense breast tissue may increase a woman's chance of developing breast cancer.[3] Also, detection of breast cancer using mammography is more difficult in women with dense breasts. The American Cancer Society estimates that approximately 80% of women fall in one of the middle two categories, while 10% have fatty breasts and another 10% have very dense breasts.

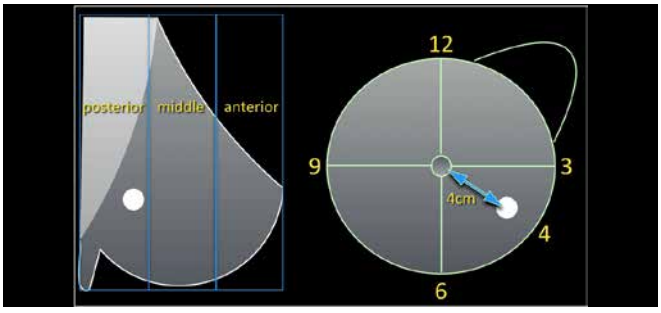
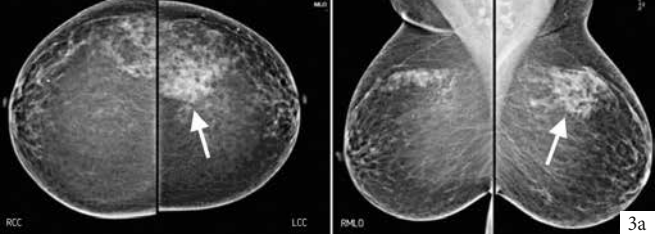
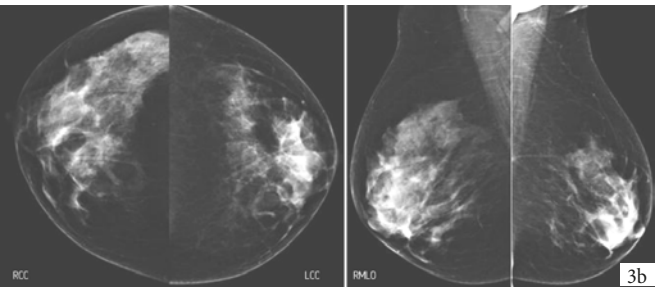


Fig 2. Lesion location reporting must include side, quadrant (upper outer, upper inner, lower outer, lower inner), clockface location (e.g. 0700), depth (anterior, middle, posterior) and distance from nipple in centimetres.





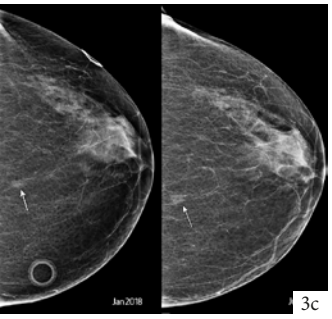


Figure 3. a. Focal *asymmetry* (arrow) appears as a denser area in less than one quadrant with no clear convex borders; this asymmetry was confirmed to be normal glandular tissue on ultrasound. **b.** Global asymmetry with the right breast containing more fibroglandular tissue than the left over an area larger than one quadrant; this is frequently a normal variant. **c.** Small asymmetry (arrow) noted in an 80 year old woman that shows growth and change in shape when reviewed 6 months later.

3. If an abnormality is noted on a mammogram:
   - Its *location* should be recorded based on laterality, quadrant and clockface location, depth and distance from the nipple (Figure 2);
   - its *characteristics* should be described; and
   - *any change* in size or characteristics from previous exams must be reported.
4. A *BI-RADS classification* is then issued based on descriptors listed in 3.
5. Finally, *Management* recommendations are made.

Section 3 in the mammogram report can only occur if an abnormality since it involves description of the lesion's characteristics; this forms the basis of the BI-RADS classification. BI-RADS scores are as follows:

BI-RADS 0: Need for further imaging or comparison with previous exams
BI-RADS 1: No abnormalities
BI-RADS 2: Benign findings
BI-RADS 3: Probably benign but cannot totally exclude malignant disease
BI-RADS 4: Suspicious findings (groups A, B and C based on increasing level of suspicion)
BI-RADS 5: Findings strongly suggestive of malignant disease
BI-RADS 6: Biopsy-proven breast cancer undergoing treatment

Lesion description is a complex exercise as the features being analysed often lie along a continuous spectrum of change rather than in clearly distinct subgroups. Here are the main lesion feature groups defined in the BI-RADS lexicon:

- **Asymmetries**: these are densities seen only in one projection or lack clear convex border on one projection. They may be *focal* (in less than one quadrant) (Figure 3a) or *global* (occupying one quadrant or more)(Figure 3b). Focal asymmetries are often due to tissue superimposition, while global asymmetries are usually normal variants. Of more concern is the *developing asymmetry*, which shows growth or change in shape over time; 15% of these are cancers (Figure 3c).
- **Mass lesions:** these are 3-dimensional lesions that are clearly seen on 2 projections and that have convex borders. They are described based on size, shape (Figure 4) and margins (Figure 5), density of nodule (low/intermediate/high) and associated findings.
- **Associated findings:** these include calcifications (Figure 6), associated distortion (Figure 7), duct changes (Figure 8), skin thickening and/or retraction (Figure 9).

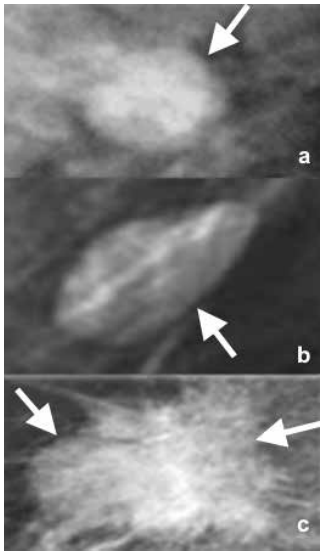
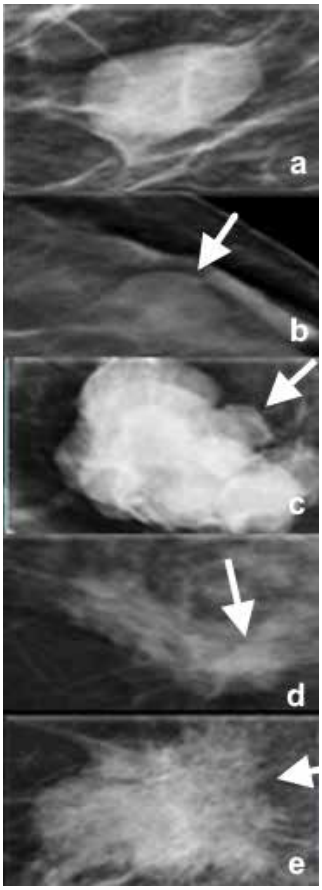


Figure 4: *Lesion shape* is classified into 3 groups: round (a), oval (b) or irregular (c). Round and oval lesions are mostly benign, while irregular lesions raise a high degree of suspicion.

Figure 5: Lesion *margins* are classified into 5 types: circumscribed (a), obscured (b), micro-lobulated (c), indistinct (d) and spiculated (e). Type a represents the lowest level of suspicion, while type e represents the highest suspicion for malignant disease.



There are many situations where there is no clear BI-RADS score that matches the imaging findings. Here are some of these situations:

- In very dense breasts with no imaging findings but poor visibility, one must score as BI-RADS 1. However, one must also recommend or proceed to further imaging such as ultrasound and in some cases MRI.
- All stable intramammary lymph nodes, benign calcifications, fat-containing lesions, implants or metallic artefacts, known benign architectural distortion (clear stability over time) are classified as BI-RADS 2.
- A score of BI-RADS 3 should be used only if findings are almost certainly benign (<2% suspicion). A radiologist should not use BI-RADS 3 if he/she is not sure. If a radiologist is unsure about a finding (>2% suspicion),

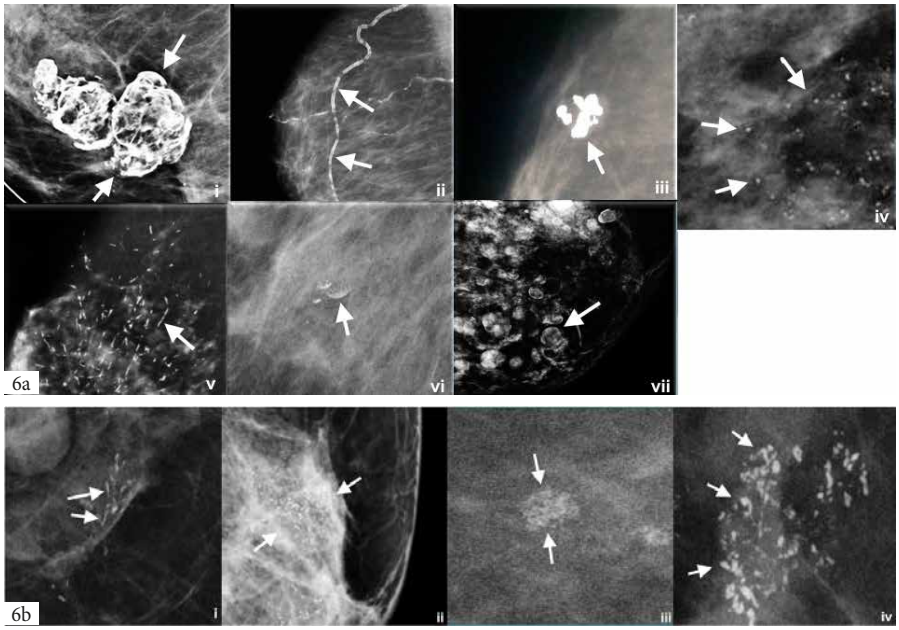


Figure 6: *Calcifications* within a lesion are classified based on their shape and size. **a**. Benign type calcifications may have the following features: macro (>1mm), central lucency (i), vascular (ii), popcorn (iii), rounded and numerous (<1mm) (iv), solid rods (v), milk of calcium (vi) and egg-shell (vii) shape. All aforementioned forms of calcification are classified as BI-RADS 2 or 3.

b. Malignant-appearing calcification are given a BI-RADS 4 classification. These include fine linear/branching/fragmented (i), pleomorphic (mixture of appearances) (ii), amorphous (iii) and coarse heterogeneous (iv).

a BI-RADS 4A score should be used and further investigation recommended; this may involve a follow-up mammogram or breast ultrasound within 6 months. Increase in size of the lesion should prompt biopsy, while decrease in size or development of benign features should reclassify the lesion to BI-RADS 2. Stable lesions should be followed with imaging.

- Unilateral axillary lymphadenopathy that is clearly benign based on mammographic findings should be classified as BI-RADS 2. If not clearly benign, this finding should be given a BI-RADS 0 score and further investigation with ultrasound should be performed. One must consider the possibilities of an occult breast cancer, lymphoma or metastatic carcinoma (such as from melanoma, other skin cancer or ovarian cancer).
- Bilateral axillary lymphadenopathy with no breast findings should be classified as BI-RADS 2 even if the patient has known lymphoma, since the BI-RADS classification is based only on findings present in the breast. However, an additional statement must be included in the recommended management section of the report stating the presence of lymphadenopathy and its underlying cause.
- If a patient has had breast cancer resection with positive resection margins (i.e. incomplete resection), but mammograms show only post-op change, a BI-RADS 2 score should be used. However, a statement relating to surgical resection margins must be included in the management statement.
- In a case of clinically evident Paget's disease of the nipple (cancer of the nipple) with no suspicious mammographic findings, one must issue a BI-RADS 2 score and add a statement about the nipple findings in the recommendations section.
- BI-RADS 0 scores should be avoided particularly if a benign-appearing lesion is present or if further imaging with breast MRI is required.

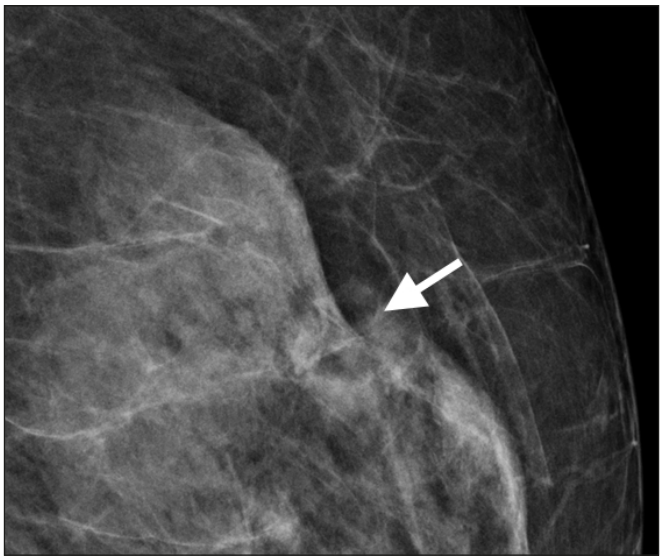


Figure 7: *Architectural Distortion* refers to any distortion of the tissue texture lines within the breast (arrow).

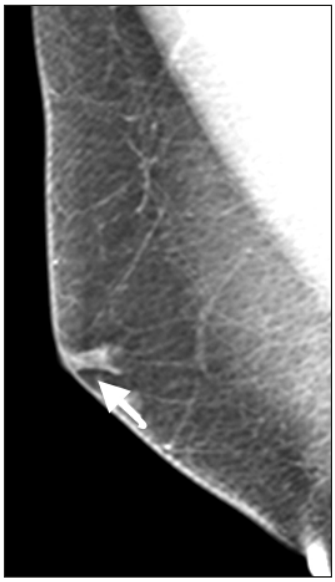


Figure 8: A solitary dilated duct (arrow) is sometimes seen on a mammogram particularly in the case of a fatty breast. In the absence of associated suspicious calcifications, this represents <2% risk for malignancy.

The significance of the BI-RADS classification lies in the relationship between the BI-RADS score and likelihood of malignant disease. The following statistical associations have been demonstrated:

BI-RADS 1 – 0% malignancy
BI-RADS 2 – 0% malignancy
BI-RADS 3 – 0-2% likelihood of malignancy
BI-RADS 4 – A 2-10% risk; B 11-50% risk; C 51-95% risk
BI-RADS 5 – >95% risk
BI-RADS 6 – Biopsy-proven malignancy under treatment

The BI-RADS classification is one of the main diagnostic tools that guides management. Significant discrepancies between pathology and BI-RADS reports do sometimes occur, and it is often the BI-RADS report that dictates further management and not the pathology report as the latter may be influenced by sampling errors.

In conclusion, the BI-RADS score and management recommendations help the breast radiologist to guide treatment and follow-up and ensures accurate communication between all breast care specialists. In addition, the BI-RADS classification provides a system for structured/systematic reporting that is particularly beneficial for training new breast radiologists. Finally, a basic understanding of the classification helps patients understand and participate in their own treatment.

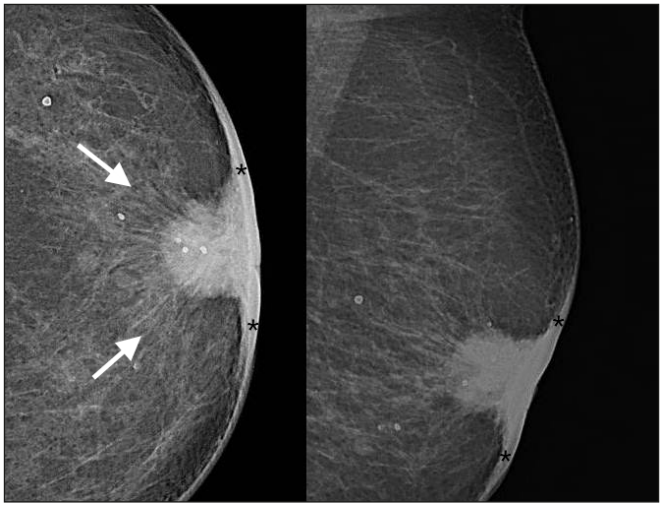


Figure 9: Spiculated retroareolar lesion (arrows) with associated skin thickening (*) due to infiltration of the nipple and adjacent skin.

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