THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

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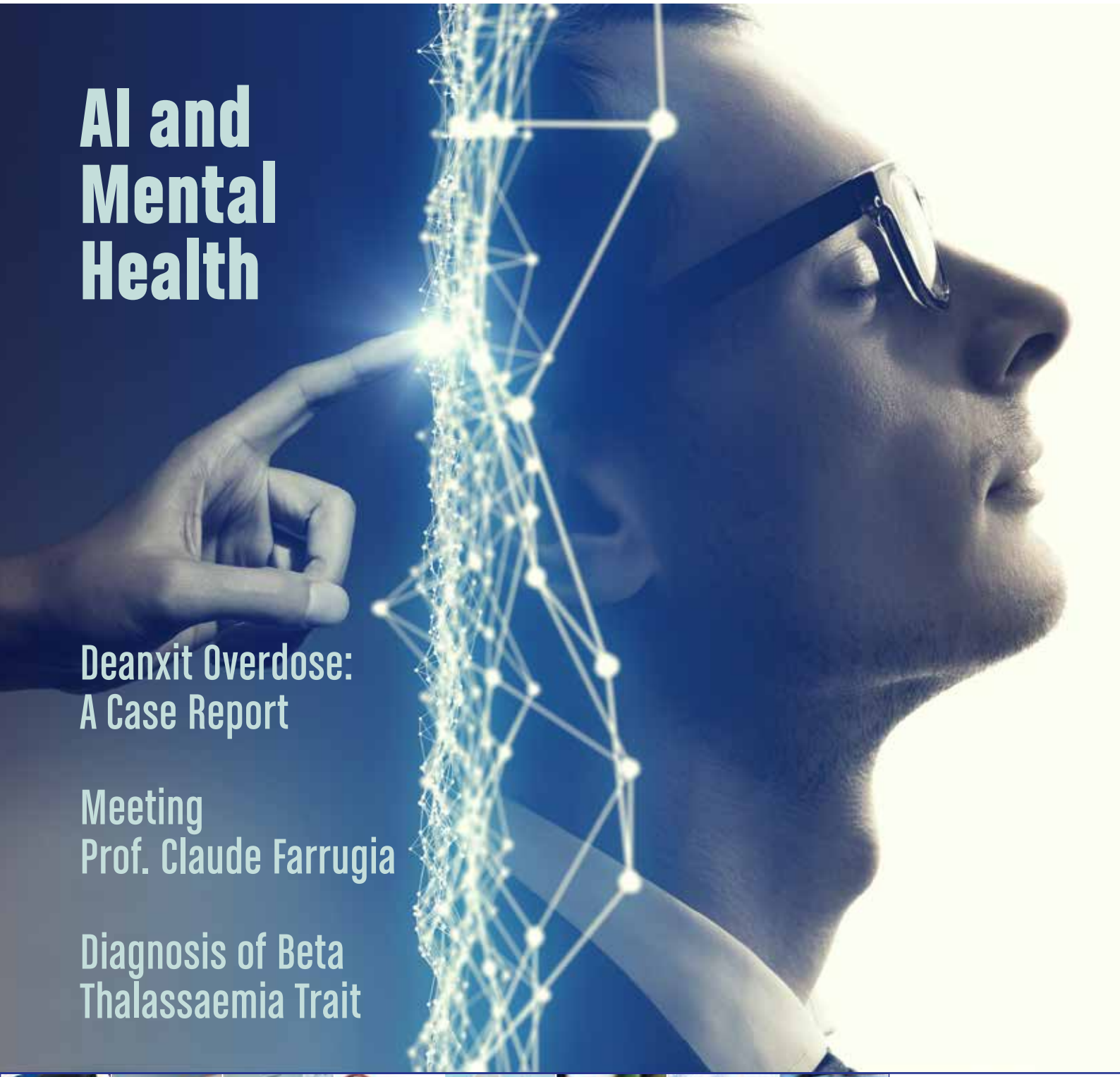


AI and Mental Health

Deanxit Overdose: A Case Report

Meeting Prof. Claude Farrugia

Diagnosis of Beta Thalassaemia Trait

SEROXAT

The Anxiolytic Antidepressant:[1,2]

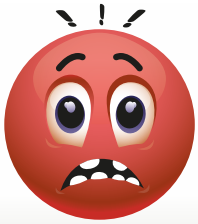
Major Depressive Disorder (MDD)[3]

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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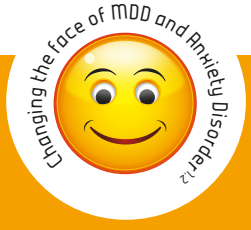

Reference: 1. Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH *et al.* Practice guideline for the treatment of patients with major depressive disorder (Third Edition) American Psychiatric Association 2010. 2. Baldwin et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology Journal of Psychopharmacology 1–37 2014. 3. Seroxat SPC March 2019.

Job No: PM-MT-PRX-ADVR-190001 Date of preparation: August 2019

HON. SILVIO SCHEMBRI Junior Minister for Financial Services, Digital Economy and Innovation within the Office of the Prime Minister

GUEST EDITORIAL

LOOKING TO THE FUTURE
THE TRANSFORMATION OF HEALTHCARE THROUGH AI

The vast field of Artificial Intelligence (AI) knows its beginnings in 1956, at a conference at Dartmouth College, in Hanover, New Hampshire, where the term 'artificial intelligence' was coined. More than six decades later AI has emerged from the laboratory, as a science project, evolving into a more consumable, commercially viable and socially impactful technological innovation.

With numerous accomplishments in the disruptive technology sector under its belt, the Maltese Government proceeded to set its sight on this relatively new science, which complemented its vision for the country's digital future. In November 2018 the Parliamentary Secretary for Financial Services, Digital Economy and Innovation Silvio Schembri appointed the **Malta.AI Taskforce**, which includes a diverse set of some of the country's best minds, with the remit of advising the Government and developing a national strategy on AI.

Less than a year later the final 'Strategy and Vision for Artificial Intelligence in Malta 2030' has been launched,[1] which firmly sets the tone for Malta to become the ultimate AI launchpad – the ultimate testbed in which local and foreign companies and entrepreneurs can develop, prototype, test and scale AI. But beyond its economic benefits, AI will also tangibly transform on an individual level the way our country lives, plays and interacts.

The strategy itself is expansive, but also explores how AI can be deployed widely across the public administration to improve citizens' experiences, expand access to public services, and directly improve well-being. Six AI pilot projects will be undertaken which will gradually infuse AI into education, healthcare and a range of public services to deliver better services to Malta's citizens and businesses, enhance economic and social well-being, and drive operational excellence across the public administration.

In the healthcare sector extensive work is underway to start using AI to detect and diagnose various forms of cancer, monitor health and provide individuals with personalised treatment plans. Through AI technologies, healthcare professionals may be able to make better, quicker and more accurate decisions in the diagnosis, treatment and care with a view to improve patient health outcomes and increase the efficiency and sustainability of healthcare systems. Malta has made significant investments to become a leader in the digital health space and is acknowledged as one of the best countries to undertake health-related AI pilot projects.

However, the intervention of AI in our daily lives raises several intricate questions, mostly of an ethical, legal and regulatory nature. It was therefore imperative that the strategy, besides cultivating the correct environment for a thriving ecosystem, also provides for a robust legal and ethical framework. This will unfailingly continue to position Malta as an AI Centre of Excellence in the near future, as well as establish the all-important trust and peace of mind amongst all stakeholders, including healthcare professionals. It is with this goal in mind that the Government has launched the world's first ever national AI certification programme. Malta has already taken a global lead in developing a regulatory and certification framework for innovative technology arrangements through the setting up of the *Malta* Digital Innovation Authority and the creation of the Innovative Technologies Arrangements and Services (ITAS) Act. This stance has borne very positive results in establishing confidence and certainty within these relatively new frontiers.

The AI certification programme aims to provide applicants with valuable recognition in the marketplace that their AI systems have been developed in an ethically aligned, transparent and socially responsible manner. Certification will be awarded following a thorough audit process undertaken by independent experts authorised by the *Malta* Digital Innovation Authority.

The Government of Malta is once again demonstrating its solid commitment in endorsing technological innovation, which in the case of AI will unfailingly position Malta as an AI Centre of Excellence and Technological Hub, ultimately paving the way for a better quality of life of all Maltese citizens – in each and every aspect of their daily lives.

1. https://malta.ai/wp-content/uploads/2019/10/Malta_The_Ultimate_AI_Launchpad_vFinal.pdf

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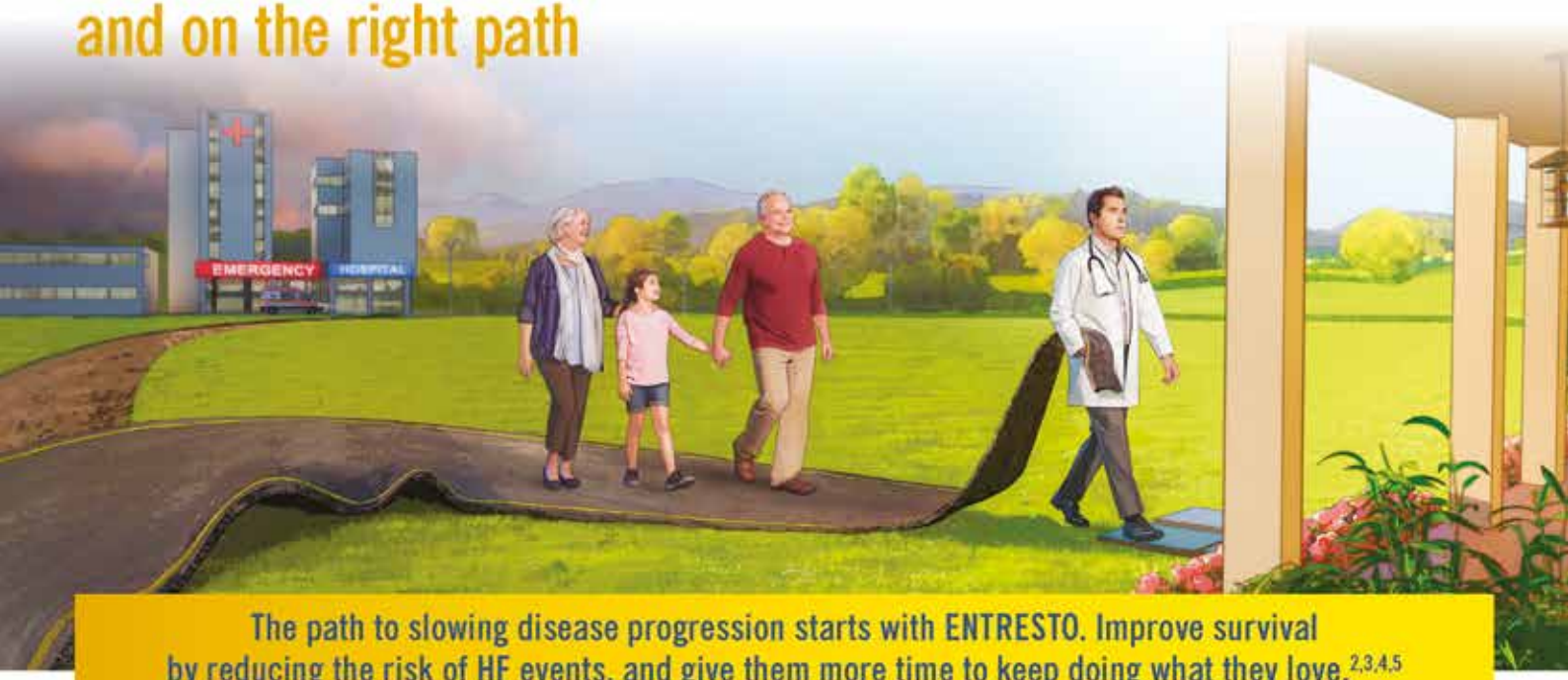
Keep HFrEF patients alive, out of the hospital, and on the right path

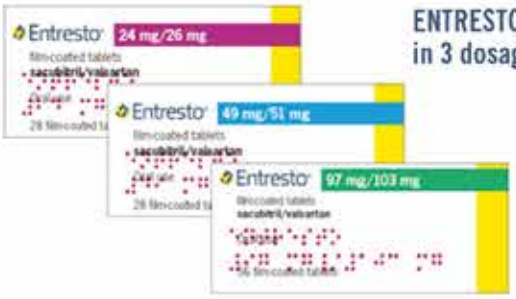


The path to slowing disease progression starts with ENTRESTO. Improve survival by reducing the risk of HF events, and give them more time to keep doing what they love.[2,3,4,5]

Start ENTRESTO today

- The starting dose is 24/26 mg or 49/51 mg, twice daily, depending on the patient's current treatment and medical condition[1]
- The target dose is 97/103 mg twice daily[1]
- Stop using an ACE inhibitor for 1.5 days (36 hours) before starting ENTRESTO[1]

ENTRESTO contains valsartan, and therefore should not be coadministered with another ARB-containing product.



ENTRESTO is available in 3 dosage strengths[1]

Before your NYHA Class II patients with HFrEF leave your office, take action with ENTRESTO—and keep them on the right path.

ENTRESTO™▼(sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. 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

References: **1.**Novartis Europharm Ltd. Entresto Summary of Product Characteristics. **2.** ENTRESTO Core Data Sheet, Version 1.2. Novartis Pharmaceuticals, July 2017. **3.** Solomon SD, et al. Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation: The PARADIGM-HF Trial. JACC Heart Fail. 2016;4(10):816-8227. **4.** McMurray JJ, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. **5.** Packer M, et al. Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure. [Abstract P1705]. Circulation. 2015;131(1):54-61.

ENT AD1 10/19 MT

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Entresto®
sacubitril/valsartan

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Dr Edith Sciberras MD graduated from the UoM in 2014 and is currently specialising in Psychiatry. Her main area of interest is women's mental health especially the perinatal period. She is also a board member in the newly established voluntary organisation *Parent-Infant Mental Health Alliance* with the aim of supporting parents and their infants, experiencing perinatal mental health issues. The co-authors of her article are Dr Joseph Cassar & Dr Maria Bezzina Xuereb.

Prof. Joseph Borg B.Sc (Hons.) MSc PhD is a biomedical scientist and molecular geneticist. He is a member of the academic staff at the Department of Applied Biomedical Science, Faculty of Health Sciences, University of Malta and author of various publications related to haemoglobin biology including two in *Nature Genetics*.

Dr Laura Grech B.Sc (Hons.) MSc PhD currently works as a post doctoral fellow with Prof. Borg in the Laboratory of Experimental Haematology and Control of Erythropoiesis, University of Malta and her research focuses on globin gene regulation and control. Together with other colleagues, Dr Grech and Prof. Borg work to discover new therapeutic avenues for haemoglobinopathies.

Dr Michelle Muscat MD MSc PGDip PhD is a Consultant Chemical Pathologist. She was successful in surgical membership and pathology fellowship exams, and has published extensively. Her areas of focus include clinical chemistry, toxicology and immunology.

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

ISSUE GUIDE

DR EDITH SCIBERRAS, DR JOSEPH CASSAR
& DR MÁRIA BEZZINA XUEREB

DEANXIT OVERDOSE
A CASE REPORT

As part of Liaison Psychiatry team at Mater Dei Hospital, in August 2019, we were called to review a 30 year old gentleman, who took an intentional overdose with suicidal intent of around 90 tablets of Flupentixol/melitracen (Deanxit). He had no other past medical history and was not on any treatment. Deanxit was initially prescribed by his family doctor in the context of anxiety and the patient only took it sporadically according to need. The overdose was carried out with leftover tablets from a prior prescription. He had not consulted his family doctor in the year after his first prescription or any psychiatrist about experiencing low mood and anxiety. He was admitted to the Coronary Care Unit at Mater Dei Hospital for cardiac monitoring due to high risk of arrhythmias. Upon psychiatric review, the patient was not easily aroused. Thereafter, he became confused and agitated, indicating delirium secondary to the Deanxit anti-cholinergic side effects. The patient was kept on a cardiac monitor and off psychotropic treatment for a few days before being transferred to the Psychiatric Unit. He was diagnosed with a moderate to severe depressive episode for which he was started on SSRIs.

Deanxit is made up of two components: flupentixol 0.5mg (antipsychotic) and melitracen 10mg (tricyclic antidepressant). Neurological side effects are mostly related to flupentixol. Very common flupentixol neurological side-effects (<1/10) include: somnolence, akathisia, hyperkinesia and hypokinesia. Common side-effects (<1/100 to <1/10) include tremor, dystonia, dizziness, headache and disturbance in attention. Uncommon (<1/1,000 to <1/100) to rare (<1/10,000 to <1/1,000) side-effects include tardive dyskinesia, dyskinesia, parkinsonism, speech disorder and convulsions. Very rare side-effects (<1/10,000) include neuroleptic malignant syndrome.[1]

However, in cases of over-dosage, anti-cholinergic symptoms related to melitracen dominate. These include mydriasis, tachycardia, urinary retention, mucosal dryness, intestinal hypomotility, irritability, agitation, hallucinations, convulsions, pyrexia, depressed level of consciousness, coma, respiratory depression, cardiac arrhythmias (ventricular arrhythmia, torsade de pointes, ventricular fibrillation), cardiac failure, hypotension, cardiogenic shock, metabolic acidosis and hypokalaemia. [2]

Self-medication with Deanxit is commonly seen in our clinical experience, however this should be recognised and prohibited. There are various other safer medications available for most of the intended applications of this drug. In any case, when used, it should only be given for a short term under the supervision of a specialist doctor.

REFERENCES

1. Fluanxol Tablets - Summary of Product Characteristics [Internet]. Retrieved 16 September 2019. Available from: www.medicines.org.uk/emc/product/998/smpc
2. Malta Medicines Authority. Summary of Product Characteristics of Deanxit [online]. Available at: http://www.medicinesauthority.gov.mt/medicine-details?id=85239 [Accessed 2 Oct 2019].

Helping people with MDD* rediscover the love for life

Treatment with Bupropion led to greater improvement in fatigue scores (p<0.01) in Bupropion remitters (-1.56) as compared to SSRI* remitters (-1.43) in MDD patients at study end point. This improvement was evident from week 4.[1]

Wellbutrin XR should not be used together with other Bupropion containing medicinal products.[2]
Wellbutrin XR tablets should be swallowed whole and not crushed or chewed.[2]

WELLBUTRIN XR ABRIDGED PRESCRIBING INFORMATION
Please refer to full Summary of Product Characteristics (SmPC) before prescribing
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. WELLBUTRIN XR is intended for oral use only. **PREGNANCY/FERTILITY/LACTATION:** *Pregnancy:* should not be used during pregnancy unless clinical condition requires treatment with bupropion and alternative treatments are not an option. *Lactation:* Bupropion and its metabolites are excreted in human breast milk. Fertility: no data on effect on human fertility. **UNDESIRABLE EFFECTS:** *Very Common* (≥1/10): Insomnia; headache; dry mouth; gastrointestinal disturbance including nausea and vomiting; *Common* (≥1/100, <1/10): Hypersensitivity reactions such as urticaria; anorexia; agitation, anxiety; tremor, dizziness, taste disorders; visual disturbance; tinnitus; increased blood pressure (sometimes severe), flushing; abdominal pain, constipation; rash, pruritus, sweating; fever, chest pain and asthenia. *Refer to the SPC for a full list of undesirable effects.* **LOCAL PRESENTATIONS:** 150mg (x30 tablets); 300mg (x30 tablets). **MARKETING AUTHORISATION NUMBER:** MA192/02301-2. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline (Ireland) Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** January 2019.
For the latest product information, please refer to the full SPC available from: gskpro.com/en-mt/products or contact us at GSK Malta (phone: +35621238131).

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Job No: PM-MT-BPR-ADVR-190002
Prepared: April 2019

References:
* **MDD:** Major Depressive Disorder; **SSRI:** Selective Serotonin Reuptake Inhibitor; Post-hoc analysis of subjects with remitted MDD on data pooled from six double blind, randomized trials comparing ≤ 300mg/day bupropion (n=169) with SSRIs (Sertraline, Paroxetine or Escitalopram) (n=324).
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2. Wellbutrin XR SPC (Nov 2018)

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AI AND MENTAL HEALTH

LUCA BONDIN & PROF. ALEXIEI DINGLI

Awareness about mental health has grown significantly in recent years, and rightly so. It is estimated that approximately 15.5% of the global population is in some way or another affected by mental illness. The increased awareness about mental health issues has led to an increased effort into tools and mechanisms to help patients with such health issues. Naturally, Artificial Intelligence (AI) research has also ventured into the area.

The application of AI in the area of patient care concerning mental health has taken various forms ranging from approaches suitable for preventing mental illnesses, to the actual care of patients already diagnosed. One of the main objectives of AI has always been to find ways of predicting future events. On these lines, several researchers have investigated various techniques to diagnose patients at risk of mental illnesses earlier and be able to start treatment immediately. Researchers are now applying the same approach to help detect early signs of mental illness.

They have adopted AI in this scenario through various means. For example, researchers from the World Well-Being Project (WWBP) are using AI to detect linguistic cues from social media that might be indicative of depression.[1] Individuals suffering from depression tend to express themselves using specific keywords such as "feelings", "I" and "me". More important, however, according to the findings of the research carried out, these traits were constant across a vast population and not just one-offs. After analyzing half a million Facebook posts, the researchers report that their algorithm was able to identify depression-associated language markers. They could predict depression up to three months before the person receives a formal diagnosis. Other researchers attempt to perform early detection of depression using other cues, such as facial expressions and the pronunciation of words. Such approaches are not limited to just identifying and diagnosing depression but also other risks like suicide.

One of the most popular approaches is the use of chatbots that can have a conversation with an individual like a human would. Questions like "How are you doing today?" or "How do you feel?" may seem like simple questions that a caring friend might ask, but through AI, nowadays we can have machines that do the same thing. The beauty of this technology is that it can be packed neatly on personal devices that can be accessed anytime.

Let us give an example. Dr Alison Darcy created Woebot,[2] a Facebook-integrated software that replicates conversations that a patient might have with his or her therapist. Such chatbots do not replace the human connection, but they offer the patient the impression that there is someone ready to listen to him day and night. While acknowledging that people prefer not to talk to machines and that this might lead to some resistance, the future of chatbots does indeed look very promising.

Finally, we want to introduce you to a new concept that is fast gathering popularity in the field of AI, especially regarding the area of care. The technologies we have available are making it possible for us to develop intelligent tools with which to provide better training for healthcare professionals. One such example is the use of virtual reality to help healthcare professionals better understand patients on the Autism Spectrum, amongst others.

Research carried out at the Department of AI within the University of Malta resulted in an application that gave parents and caregivers the chance to experience the world through the eyes of autistic children, using virtual reality. Through it, they could relive a day in their lives and gain precious insights on the challenges which these children face. The results of this study were rather astonishing. After using the experience, people felt more empathetic, and in general, they reported that they could better understand these children.

The same concept can also be applied to other cases. The researchers at the Department of AI are currently creating a new experience of patients suffering from other mental illnesses such as schizophrenia.

In synthesis, AI has the potential to provide the critical resources required to help provide better care to patients. As AI tools progress, we are required to ensure that measures are put in place to make them safe and effective, especially for the most vulnerable patients. What is clear is that the implementation of AI in this setting can be a gamechanger which helps both patients and caregivers achieve their mutual goals.

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children aged 2 to 5 years [1-3]	2.5ml every 4-6hrs as required
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OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: Please refer to full Summary of Product Characteristics **(SPC)** before prescribing. **TRADE NAME: ACTIFED. ACTIVE INGREDIENT:** Actifed **DM** Cough Linctus**:** Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; Actifed Syrup**:** Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; Actifed Expectorant**:** Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Guaiphenesin 100mg. **PHARMACEUTICAL FORM:** Oral Solution **INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of**:** Actifed **DM** Linctus**:** a nasal decongestant, an anti-histamine and an antitussive; Actifed Syrup**:** a nasal decongestant, and an anti-histamine; Actifed Expectorant**:** a nasal decongestant, an anti-histamine and an expectorant. **DOSAGE:** please refer to full **SPC**. Actifed **DM** Cough Linctus, Actifed Syrup and Actifed Expectorant are authorised for use without the need of a medical prescription in Adults and Children over 12 years. In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor. **CONTRAINDICATIONS:** Previous intolerance to any of the active substances; use of **MAOI**'s in the preceding two weeks; severe hypertension or heart disease; concomitant use of pseudoephedrine can cause a rise in blood pressure. **PRECAUTIONS:** May cause drowsiness; avoid the concomitant use of alcohol or other centrally active sedatives; use with caution in patients with liver impairment or moderate to severe renal impairment. **INTERACTIONS:** Sympathomimetics; **MAOI**'s. **ADVERSE EVENTS:** Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and rarely hallucinations have also been reported; skin rashes, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement. **PREGNANCY AND LACTATION:** Administration should only be considered if the expected benefits to the mother outweigh the potential risks to foetus or child. **PRESENTATION: DM**Cough Linctus, Expectorant, Syrup**:** Amber glass bottle x 100ml.**M**arketing **A**uthorisation Holder**: G**laxo**S**mith**K**line**(I**reland**)** Ltd. **M**arketing **A**uthorisation **N**umber**: MA** 192/02001-6. Legal category**: POM – A**ctifed **DM** Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years. Date of preparation**: O**ctober 2019.

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References: 1. Actifed Syrup SPC (Nov 2018); 2. Actifed DM Cough Linctus SPC (Nov 2018); 3. Actifed Expectorant SPC (Mar 2019); 4. Actifed Syrup SPC OTC (Nov 2018); 5. Actifed DM Cough Linctus SPC OTC (Nov 2018); 6. Actifed Expectorant SPC OTC (Mar 2019)

PM-MT-NA-ADVR-190001 Prepared: October 2019

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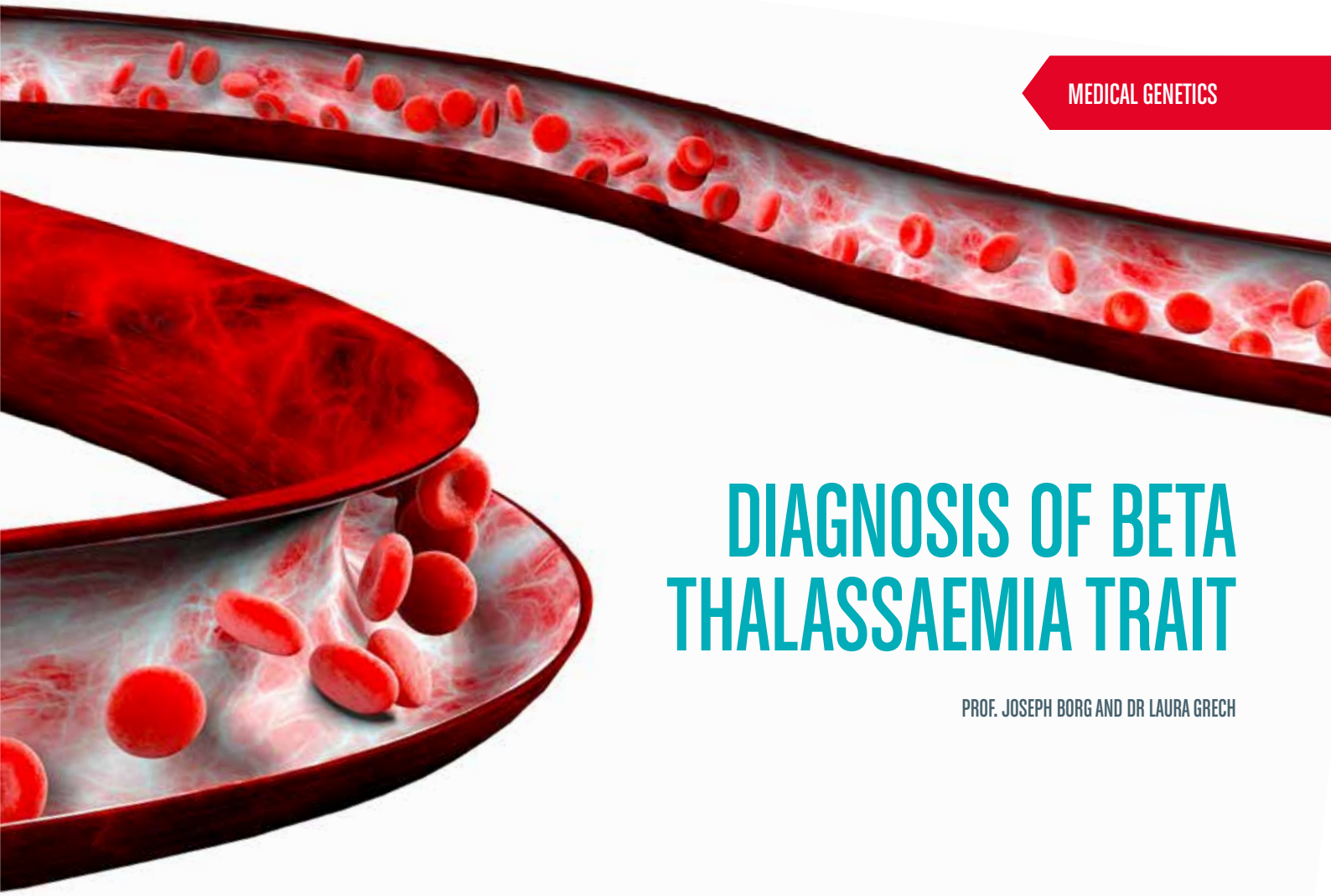

DIAGNOSIS OF BETA THALASSAEMIA TRAIT

PROF. JOSEPH BORG AND DR LAURA GRECH

HAEMOGLOBIN

Haemoglobin (Hb) is chemically best considered as a duplex of globin heterodimers. The main adult haemoglobin (HbA) is composed of two alpha (α) and two beta (β) chains assembled in two αβ dimers ($\alpha_1\beta_1$ and $\alpha_2\beta_2$), while foetal haemoglobin (HbF) is composed of two alpha-gamma (αγ) dimers.[1] Their main function is to transport oxygen from the lungs to tissues, but it also specifically interacts with three other gases, carbon dioxide, carbon monoxide and nitric oxide.

The α chains are located on the short arm of chromosome 11 while the β chains are located on the short arm of chromosome 16. In the first stages of human development, embryonic haemoglobin consisting of two heterodimers of ε and ζ-globin chains is expressed in red blood cell progenitors (figure 1). At 12 weeks post-conception, as the site of erythropoiesis changes from the yolk sac to foetal liver the first switch in globin composition occurs. The embryonic haemoglobin is replaced by HbF consisting of α- and γ- globin chains.[2] Around birth as erythropoiesis starts taking place in the bone marrow and spleen, the second globin switch occurs. This results in the decline of HbF synthesis together with increased synthesis of adult haemoglobin composed of HbA ($\alpha_2\beta_2$) with a minor HbA_2 ($\alpha_2\delta_2$).[3,4] Residual amounts of HbF continue to be synthesized throughout adult life and expressed by F-erythrocytes.[5] In most adults, F-erythrocytes contain less than 2% of total Hb, although there is considerable variation[6] (figure 1).

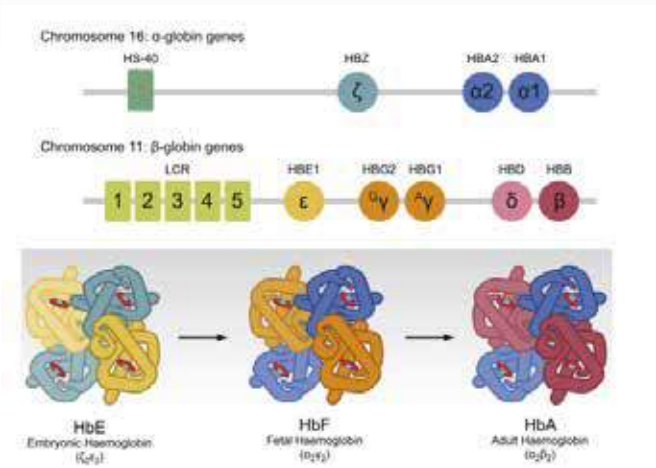

Figure 1: The α-like globin genes are found on chromosome 16 and the β-like globin genes are found on chromosome 11. During human development, the composition of haemoglobin changes from an embryonic form made of ζ- and ε-globin to a foetal form made up of α- and γ-globin and finally to an adult form made up of α- and β-globin (figure adapted from Diepstraten and Hart, 2019).[7]

HAEMOGLOBINOPATHIES

Mutations in the beta globin gene can give rise to haemoglobinopathies. Haemoglobinopathies are the commonest monogenic disorders, affecting about 7% of the world's populations.[8] The haemoglobinopathies can be classified as (i) the structural variants such as Sickle cell disease (HbS), haemoglobin C (HbC) and Haemoglobin E (HbE),

β-THALASSAEMIA IS MOST COMMONLY PRESENT IN PERSONS OF MEDITERRANEAN, AFRICAN AND SOUTHEAST ASIAN DESCENT

(ii) thalassaemia which can be further sub-classified into α, β, δβ and εγδβ thalassaemia depending on the particular globin chain or chains that is/are ineffective synthesized, and (iii) Hereditary Persistence of Foetal Haemoglobin (HPFH) in which there is a defect in the normal switch from foetal to adult haemoglobin.[9]

BETA-THALASSAEMIA

β-thalassaemia is most commonly present in persons of Mediterranean, African and Southeast Asian descent. β-thalassaemia can be divided into three main forms which are the β-thalassaemia major also known as Cooley anaemia, β-thalassaemia Intermedia and β-thalassaemia minor also called β-thalassaemia trait or β-thalassaemia carrier. It is the result of deficient or absent synthesis of beta globin chains which are controlled by one gene on each chromosome 11. The degree of globin chain reduction is determined by the nature of the mutation in the β-globin gene.[10] In the Maltese population, the most common mutations are the IVS1-6C, IVS1-110A, IVSII-1A and COD39T.[11] The β+ IVS1-6C mutation is the most predominant β-thalassaemia mutation in the Maltese population.[12]

DIAGNOSIS OF BETA-THALASSAEMIA TRAIT

The diagnosis of β-thalassaemia begins with suspicion of the disease in anaemic patients based on phenotype, family history and relevant laboratory screening. The detection and characterisation involve a 3 tier-work up: (1) Complete blood count and picture, (ii) Special haematological tests, and (iii) DNA testing.

1. COMPLETE BLOOD COUNT AND PICTURE

For screening of β-thalassaemia, the mean corpuscular volume (MCV) of less than 80fL and/or mean corpuscular haemoglobin (MCH) value of less than 26pg are usually used as cut-off levels for a positive screening result. The mean corpuscular haemoglobin concentration (MCHC) is usually normal. The advantages of thalassaemia screening by MCV and MCH are the rapid, cost effective, reproducibility and accurate analysis.[13] One has to keep in mind that several conditions such as iron deficiency anaemia and anaemia of inflammation can also results in low MCV and MCH. Also, normal ranges of MCV vary by age in infants and young children. On the other hand, the interaction of β-thalassaemia trait with α-thalassaemia trait alone or together with glucose-6-phosphate dehydrogenase deficiency may lead to normal MCV and gives a false-negative result for thalassaemia screening.[13]

The haemoglobin concentration can be normal or slightly reduced in β-thalassaemia carriers while the red blood cell (RBC) count can be elevated. The red cell distribution width (RDW) is a measure of the degree of variations in red cell size, and an increase in RDW can be noticed in β-thalassaemia carriers.[14] In β-thalassaemia carriers, the blood film varies from almost normal, with only mild microcytosis, to markedly abnormal. In addition to microcytosis abnormal features can include anisocytosis, hypochromia and poikilocytosis. Prominent basophilic stippling and target cells can be seen in individuals with a more severe phenotype.

Screening of thalassemia carriers by using RBC indices alone in a population with a high prevalence of β-thalassemia is not sufficient and other techniques such as haemoglobin analysis and DNA testing are required.

2. HAEMOGLOBIN ANALYSIS

Haemoglobin analysis is an important laboratory evaluation to provide a presumptive identification and diagnosis of β-thalassaemia. There are several platforms for haemoglobin analysis including haemoglobin electrophoresis using cellulose acetate membrane, acid agarose or citrate agar gel, isoelectric focusing (IEF), high performance liquid chromatography (HPLC) and capillary electrophoresis. Each method uses different principles to separate different species of haemoglobin molecules.[15] In Malta for the diagnosis of the β-thalassaemia trait we use the IEF together with HPLC.

Isoelectric focusing

IEF uses a polyacrylamide or agarose gel containing low molecular weight molecules. These molecules allow the establishment of a pH gradient; for separation of haemoglobins the pH ranges from 6-8. When an electric current is applied to the gel, the amphoteric molecules migrate through the gel to their isoelectric points along the gel. In doing so they form a stable pH gradient. Haemoglobin variants also exhibit this characteristic. They migrate through the gel until they reach the area in which their individual isoelectric point is equal to the corresponding pH on the gel. When these occur the charges on the variants are 0 and therefore migration ceases. The electric field counteracts diffusion and the haemoglobin variant forms a discrete thin band. The different Hb variants have different isoelectric point and thus they separate out on the gel to form bands at specific positions. The bands are then stained.[15] In β-thalassaemia carriers the HbA is reduced while HbF and HbA_2 are slightly increased

High performance liquid chromatography

HPLC technique is a method used to separate compounds or molecules on the basis of their chemical characteristics. Separation of Haemoglobin is carried out using the VARIANT β-thalassaemia Short Program which utilizes the principles of cation-exchange HPLC. The HPLC rapidly and accurately measures HbA_2 which often provides a diagnostic clue to the presence of β-thalassaemia trait especially when this is found with hypochromic, microcytic erythrocytes.

The increase in HbA_2 in β-thalassaemia carriers is a result of both transcriptional and post-transcriptional effects and an increase of more than 3.2% can indicate the presence of β-thalassaemia trait (figure 2). In β-thalassaemia carriers the HbA_2 levels vary according to the thalassaemia mutation. Small deletions of the 5' portion of the beta globin gene are associated with the highest HbA_2 levels. In fact, an HbA_2 of 7-9% is seen in heterozygotes that have deletions that involves the remove of the beta globin promoter.[16,17]

From studies it is now clear that increases in HbA_2 may not be a constant accompaniment of β-thalassaemia trait. β-thalassaemia trait patients who also have iron deficiency have slightly reduced but still elevated HbA_2 but β-thalassaemia trait individuals with severe iron deficiency can have reduced HbA_2 levels (less than 3.0%).[17] On the other hand, individuals with variants in *KLF1* can also have an increase in HbA_2 levels and if their HbA_2 levels fall between 3.3% and 3.9% it is important that these subjects are not classified as β-thalassaemia trait.[18,19]

3. DNA ANALYSIS

β-thalassaemia is mainly caused by mutations in globin gene and therefore the most definitive diagnosis for β-thalassaemia is the molecular analysis of the beta globin sequence (figure 3). Many different molecular techniques are used to detect beta globin mutations. These molecular techniques can be grouped by the mutation type they target: (i) detection methods for structural variations such as gene deletion and duplication, and (ii) detection methods for sequence variations such as nucleotide substitution, insertion or short insertion/deletions.[20]

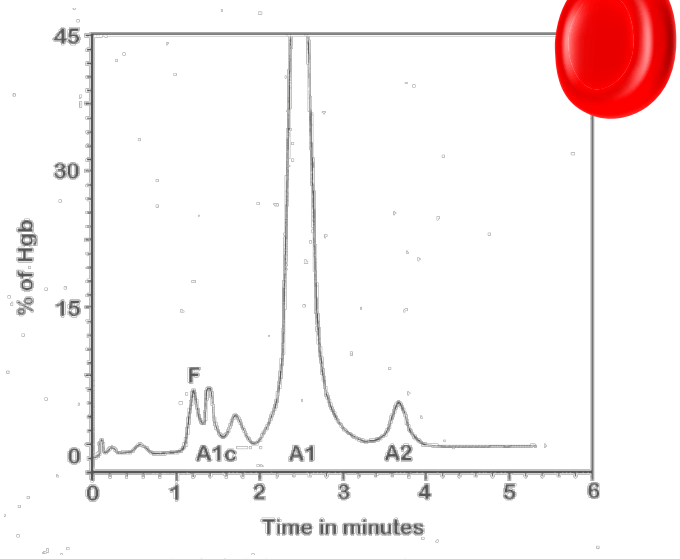

Figure 2: HPLC result of a β-thalassemia carrier showing an increase in HbA_2 and HbF (Source: HPLC chromatogram provided by the Laboratory of Molecular Genetics, University of Malta)

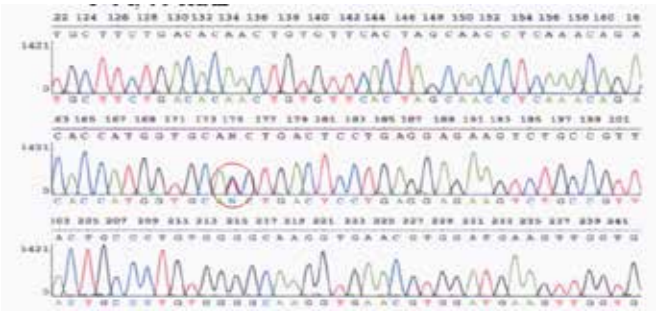

Figure 3: DNA sequence of the beta globin gene showing the IVS1-6C mutation circled in red. (Source: Laboratory of Molecular Genetics, University of Malta)

CONCLUSION

β-thalassaemia mutations are inherited in an autosomal recessive manner. Two β-thalassaemia heterozygote parents have a 25% chance of having a β-thalassaemia major child and thus, proper diagnosis of β-thalassaemia trait is important. Diagnosis of β-thalassaemia requires a comprehensive evaluation combining red blood cell phenotypes, haemoglobin profiles and DNA analysis.

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Treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine. Aimovig is for subcutaneous use. Aimovig is intended for patient self administration after appropriate training. The injection can be administered into the abdomen, thigh or into the outer area of the upper arm. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard.

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

WARNINGS AND PRECAUTIONS:
♦ Patients with certain major cardiovascular diseases were excluded from clinical studies. No safety data are available in these patients. ♦ In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. ♦ In patients with latex sensitivity: The removable cap of the Aimovig pre-filled syringe/pen contains dry natural rubber latex, which may cause allergic reactions in individuals sensitive to latex.

INTERACTIONS:
No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies. No interaction with oral contraceptives (ethyl estradiol/norgestimate) or sumatriptan was observed in studies with healthy volunteers.

ADVERSE REACTIONS:
Common (≥1 to <10%): Hypersensitivity reactions including rash, swelling/oedema and urticaria, Constipation, Pruritis, Muscle Spasms, Injection site reactions.
Please consult the Summary of Product Characteristics for a detailed listing of all adverse events before prescribing.

PREGNANCY, LACTATION AND FERTILITY:
Pregnancy: There are a limited amount of data from the use of erenumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Aimovig during pregnancy. **Lactation:** It is unknown whether erunumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, use of Aimovig could be considered during breast-feeding only if clinically needed. **Fertility:** Animal studies showed no impact on female and male fertility.

LEGAL CATEGORY: POM

PACK SIZE: 1 pre-filled pen 70mg, 140mg

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBER:
1 pre-filled pen 70mg (EU/1/18/1293/001)
1 pre-filled pen 140mg (EU/1/18/1293/004)

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

2019-MT-AIM-23-AUG-2019

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IS DIETARY ANIMAL PROTEIN CARCINOGENIC?

PROF. ALBERT CILIA-VINCENTI

The little nutritional science taught at conventional medical schools emphasises the notion that animal protein is the highest quality nutrient needed on a regular basis to build and maintain a healthy body. The word protein in fact comes from the Greek *proteios*, meaning "of prime importance". There have also been recent fad diets recommending only meats, eggs and cheeses, and no carbohydrates, to lose weight. To be on the safe side, most doctors would recommend a "balanced" diet, whatever "balanced" actually translates to at breakfast, lunch and supper.

This feature will therefore come as a surprise, outlining decades of published research pointing towards too much animal-based foods being the most important risk factor for the major types of cancer in both sexes. The farming lobbies are often accused of efforts to hinder exposure of these claims.

In 1968 an Indian research paper reported an experiment measuring hepatocellular carcinoma rates and protein consumption in two groups of laboratory rats. One group was given aflatoxin (a strong liver carcinogen) and diets containing 20% protein. The second group was given the same amount of aflatoxin and diets with only 5% protein. All the rats fed 20% protein got liver cancer or its precursor lesions, but not a single animal fed 5% protein got liver cancer or premalignant changes. An incredible 100% versus 0%. The protein used was cow's milk casein.[1]

Earlier, doctors in the Philippines claimed that hepatocellular carcinoma was more common in children than adults, compared to being commonest after 40 years of age in the West, and that the incidence of paediatric hepatic carcinoma was higher in rich best-fed Philippines families, possibly because they were eating much more animal protein than poor families.[2]

When the media reports a new chemical carcinogen, the public reaction is swift. In 1989 an apple industry growth regulator chemical (Alar) in the US was reported as "the most potent carcinogen in the food supply".[3,4] One woman called state police to chase a school bus and confiscate her child's apple, schools stopped serving apples, Alar use was halted, and the apple industry suffered a staggering financial loss.[5]

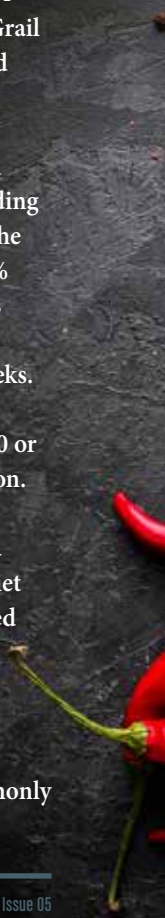
Sodium nitrite had been used as a meat preservative since the 1920s.[6] In 1970, the journal *Nature* reported that dietary nitrite may form nitrosamines in the body.[7] The US National Toxicology Program had declared that nitrosamines are "reasonably anticipated to be human carcinogens".[8,9] One nitrosamine, NSAR (N-nitrososarcosine), was given to 20 rats divided into two groups, one group getting twice the NSAR dose of the other group. Only 35% of rats on the low dose got throat cancer. All higher dose rats died of cancer in the second experiment year.[9] How much NSAR did the rats get? The low dose was equivalent to the NSAR a human would ingest by eating 270,000 sandwiches, each containing 500g cured ham, every day for over 30 years.[10] In another study, 10.2% of rats fed nitrite got lymphoma while only 5.4% of control animals not fed nitrite got lymphoma.[11] This created a public outcry. Marginal scientific results in animals fed exceptionally high levels of chemical for half their lifespan can make big waves in the public's perception but, when the dust settled, industry cut back on nitrite usage and the issue fell out of the spotlight.

The point does not relate to the safety of nitrite, but the mere possibility, however unlikely it may be, that it could cause cancer which alarms the public. So what if there was a chemical that experimentally turned on cancer in 100% of test animals and its relative absence limited cancer to 0% of the animals? Finding such a chemical would be the Holy Grail of cancer research. This is exactly what the aforementioned Indian research paper had claimed.[1]

The Indian animal experiment, whose results were initially not accepted by American scientists, was repeated and expanded upon in America. The effects of protein feeding on tumour development were spectacular and replicated the Indian findings. All rats administered aflatoxin, but fed 5% protein diet, were alive and active at 100 weeks and all rats given the same level of aflatoxin, and fed 20% protein diet, were either dead or moribund from liver cancer at 100 weeks. Again, the protein used was cow's milk casein.[12,13]

Furthermore, the diets of some rats were switched at 40 or 60 weeks to investigate the reversibility of cancer promotion. Animals switched from a high-protein to a low-protein diet had about 40% less tumour growth than animals fed a high-protein diet. Animals switched from a low-protein diet to a high-protein diet halfway through their lifetime started growing tumours. These findings confirmed nutritional manipulation can turn cancer "on" and "off".[12,13]

Cow's milk protein is undoubtedly a potent cancer promoter in rats dosed with aflatoxin. The fact that this promotion occurs at dietary protein levels (10-20%) commonly

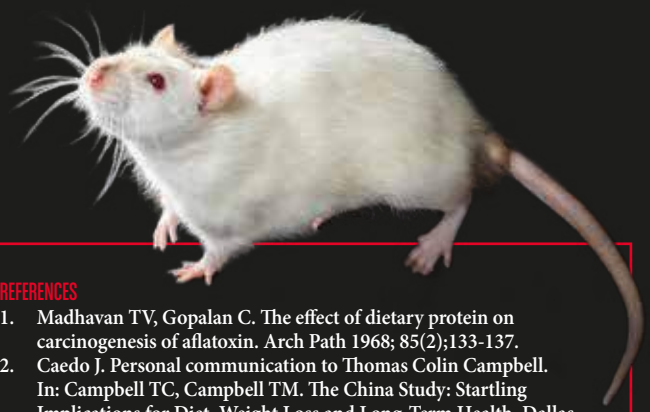


> "HE WHO DOES NOT KNOW FOOD, HOW CAN HE UNDERSTAND THE DISEASES OF MAN?"
>
> HIPPOCRATES

used both in rodents and humans makes it especially provocative. So how does this research apply to human health and human liver cancer in particular? If casein's effect on cancer promotion is consistent across other species, other carcinogens and other organs, it might also apply to humans. Furthermore, and of great significance, experiments with plant protein (wheat and soya) did not promote tumour growth, even when fed high levels.[14]

In 1975 and 1982, studies claimed that chronic hepatitis B virus (HBV) infection was a major risk factor (20-40 times increased risk) for human liver cancer.[15,16] Researchers argued that both aflatoxin and HBV were key causes of human liver cancer but no one dared suggest that nutrition had anything to do with this disease. However, a subsequent study using two strains of transgenic HBV-transfected mice showed a similar result to the rat aflatoxin study. A 22% casein diet turned on expression of the viral gene to cause cancer, whereas a 6% casein diet showed almost no such activity.[17,18] It could now be concluded that cow's milk protein dramatically promotes liver cancer in rats dosed with aflatoxin and in mice infected with HBV.

Another study in rats dosed with two carcinogens showed that increasing intakes of casein promoted mammary cancer.[19] More studies used fish protein, dietary fats and carotenoid antioxidants, measuring the ability of these nutrients to promote liver and pancreatic cancer, thus proving nutrition controlled cancer evolution far more than the dose of the initiating carcinogen.[20]



Although there were strong arguments that these provocative findings were *qualitatively* relevant to humans, their *quantitative* relevance was unknown. In other words, is the animal protein and cancer relationship important for all humans in all situations, or is it marginally important for a minority of people in unique situations? Is this causative relationship responsible for one thousand, one million or more human cancers annually? The answer needed direct evidence from human research. This came from the so-called China Study, which The New York Times described as the "Grand Prix of Epidemiology", and "a story that needs to be heard" according to Robert C. Richardson, professor of Physics, Provost of Research at Cornell University and Nobel Prize Winner. Another feature will outline its findings.

Because nobody was taught the above at their medical school, readers might find its claims difficult to accept, also because the published material referred to is a few decades old. The American scientist (T. Colin Campbell PhD) leading these laboratory and epidemiological studies is the son of a farmer and, as would be expected, he originally dismissed the Indian paper (claiming animal protein is a cancer promotor) as bad research. So, as a good researcher would do, he repeated the Indian animal experiment and found its claim to be correct. I am unaware of any more recent published research disproving the above experimental claims of a relationship between dietary animal protein and cancer promotion.

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Please refer to full SmPC for detailed information.

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ZINC Code: MLT_GIB/FFT/0005/18 Date of preparation: April 2018

Relvar Ellipta was developed in collaboration with INNOVIVA

References: 1. Bernstein DI, Bateman ED, Woodcock A, Toler WT, Forth R, Jacques L, *et al.* Fluticasone furoate (FF)/ vilanterol (100/25mcg or 200/25mcg) or FF (100mcg) in persistent asthma. *J Asthma* 2015;52(10):1073–1083. **2.** Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, *et al.* Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open label, parallel group, randomised controlled trial. *Lancet* 2017; doi.org/10.1016/S0140-6736(17)32397-8. **3.** Relvar SmPC, March 2018.

RELVAR ELLIPTA ABRIDGED PRESCRIBING INFORMATION

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

TRADE NAME: Relvar Ellipta. **ACTIVE INGREDIENT:** *92mcg/22mcg dose:* 92mcg fluticasone furoate, 22mcg vilanterol (as trifenatate). *184mcg/22mcg dose*: 184mcg fluticasone furoate / 22mcg vilanterol (as trifenatate). **PHARMACEUTICAL FORM:** Inhalation powder, pre-dispensed. **INDICATIONS:** ***Asthma*** *(92/22mcg dose & 184/22mcg dose):* Regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists and patients already adequately controlled on both inhaled corticosteroid and long-acting beta$_2$-agonist. **COPD** (92/22mcg dose): For symptomatic treatment of adults with COPD with a FEV$_1$<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. **POSOLOGY:** *For Asthma*: One inhalation, once daily. *For COPD*: One inhalation of 92/22mcg dose, once daily. 184/22mcg is not indicated for patients with COPD. Relvar Ellipta should be administered at the same time of day, each day. *Refer to full SPC for full dosage recommendations.* **CONTRAINDICATIONS:** Hypersensitivity to active ingredients / excipients. **PRECAUTIONS:** Should not be used to treat acute asthma symptoms or acute exacerbation in COPD; Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing; Caution for use in severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium; Moderate to severe hepatic impairment: 92/22mcg dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions; Systemic corticosteroid effects may occur, particularly at high doses for long periods. Caution in patients with pulmonary tuberculosis or chronic or untreated infections; Blurred vision or other visual disturbances: referral to ophthalmologist for evaluation should be considered; Caution in diabetic patients; Physicians should remain vigilant for possible development of pneumonia in patients with COPD (clinical features overlap); Incidence of pneumonia in asthma common at higher dose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. **PREGNANCY/FERTILITY/LACTATION:** *Pregnancy:* only if expected benefit to mother outweighs risk to foetus. *Lactation:* consider benefit of breast feeding child and benefit of therapy for woman. *Fertility:* No data. **UNDESIRABLE EFFECTS:** *Very common (≥1/10):* headache, nasopharyngitis. *Common (≥1/100 & <1/10):* pneumonia, upper respiratory tract infetion, bronchitis, influenza, candiasis of mouth and throat. Oropharyngeal pain, Sinusitis, Pharyngitis, Rhinitis, Cough, Dysphonia, Abdominal pain, Arthralgia, Back pain, Fractures, Muscle spasms, pyrexia. *Refer to the SPC for full list of undesirable effects.* **LOCAL PRESENTATION:** Inhaler x 30 doses. **MARKETING AUTHORISATION NUMBER:** EU/1/13/886/001-6. **MARKETING AUTHORISATION HOLDER:** Glaxo Group Limited. **LEGAL CATEGORY:** POM. **DATE OF PREPARATION:** March 2018.

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)
Malta: alternatively, any suspected AEs and medication errors can be reported via the Medicines Authority Adverse Drug Reactions reporting website: www.medicinesauthority.gov.mt/adrportal
Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

SHAMANS AND BEYOND... AYAHUASCA

DR MICHELLE MUSCAT

Ayahuasca is a psychedelic Amazonian ceremonial decoction or 'liana of the soul' containing *Banisteriopsis caapi* vine having alkaloids that cause monoamine oxidase inhibition. Another typical component is *Psychotria viridis* which contains dimethyltryptamine (DMT). The exact nature of the admixture brew may vary from place to place. Ayahuasca has also moved from shamans to recreational usage. There are both known religious and recreational uses for this herbal brew. It has hallucinogenic effects; the brew can induce out-of-body experiences and alter a person's state of consciousness. These effects stem from ayahuasca's effect on the serotonergic system.

The participation in ayahuasca rituals has been investigated by various authors. Studies specifically looked into the potential use of ayahuasca in cases of treatment-resistant depression, where it showed potential antidepressant properties.[1-3] Different authors proposed other therapeutic uses, such as in mindfulness training,[4] emotional regulation,[5] eating disorders[6] and it has also been hypothesised as potentially useful against traumatic memories[7] and specific cases of drug dependence.[8,9] In 2019, Ona et al. boldly reported that the prolonged controlled use of ayahuasca could have a positive effect on the QoL and psychological well-being of users.[10] Another study which included 22 participants and assessed biochemical parameters in the setting of chronic ritualistic ayahuasca use, twice monthly or more for the minimum of one year, did not demonstrate derangements in hepatic function.[11] Nonetheless, ayahuasca usage is inherently associated with vomiting, amongst other non-entheogenic reported effects. The vomiting is caused primarily from the effects on area postrema, found in the medulla oblongata, which controls vomiting.

It is of note that specific drug interactions may result in serious adverse effects; one such example is the serotonin syndrome which arises when ayahuasca is combined with SSRIs.[12]

Although various papers have put forth different uses for ayahuasca, on the other hand biomedical research investigating discriminative learning in zebrafish has shown that prolonged exposure to low concentrations may indeed cause harmful effects to learning and memory processes.[13] Another concern relates to possible mutagenic effects.[14] Furthermore, rat models have demonstrated foetal developmental toxicity.[15,16]

These are just some of the documented effects. Further studies into the neuroscience and neurophysiology behind ayahuasca may yield a more precise risk-benefit analysis.[17-19]

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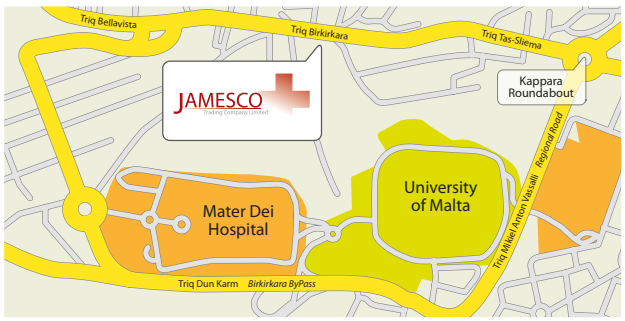

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WHEN POSITIVES MEET NEGATIVES

Dr Ian Ellul meets **Prof. Claude Farrugia**, distinguished pharmacist and Associate Professor of Chemistry at the University of Malta. Prof. Farrugia is also President of the European Industrial Pharmacists Group.

YOU GRADUATED AS PHARMACIST IN 1991. AFTER THREE YEARS YOU WERE AWARDED A SCHOLARSHIP BY THE UOM TO PURSUE YOUR STUDIES AT THE INSTITUTE FOR TUBERCULOSIS RESEARCH, UNIVERSITY OF ILLINOIS. YOU OBTAINED YOUR PHD IN PHARMACEUTICS IN 1998. WHY DID YOU CHOOSE PHARMACEUTICS?

The scholarship was related to pharmaceutics, which I must admit was fortuitous since of all the core sciences, Chemistry was my favourite subject. In hindsight I realise that my pharmacy background gave me the opportunity to approach chemistry from a different perspective; and indeed, this has offered a plethora of intriguing challenges along the years.

AFTER COMING BACK, YOU LECTURED IN CHEMISTRY FOR SIX YEARS AT JUNIOR COLLEGE; YOU THEN MOVED ON TO THE UOM. WHAT MOTIVATED YOU TO MAKE THIS CHANGE? ANY THOUGHTS IN HINDSIGHT?

The objective of reading for a PhD was precisely that of continuing to conduct research locally. At that time I must admit that I had a quixotic view of what research entails. However, I was fortunate enough to get involved in the pharmaceutical industry which provided a forum to carry out research in an applied manner to address the challenges which the local industry faces.

YOUR NAME IS INHERENTLY ASSOCIATED WITH THE LOCAL PHARMACEUTICAL INDUSTRY; INDEED, FOR THE PAST 15 YEARS YOU HAVE HELD THE POSITION OF PRESIDENT OF THE MALTA QUALIFIED PERSONS ASSOCIATION. HOW DID YOU SEE THE ROLE OF MQPA CHANGE DURING THESE LAST 15 YEARS?

Initially Qualified Persons (QPs) were represented by the Chamber of Pharmacists. However, there were a number of QPs who were non-pharmacists which equally needed representation, without any professional distinction. This is why we set up the MQPA. Obviously we kept an amicable and productive relationship with the Chamber. In recent years we also secured professional representation in the Pharmacy Council when the Health Care Professions Act (Cap 464) was revised.

The role of the Association remains essentially the same - that of supporting QPs and maintaining high professional standards; however, it has diversified in view of the new challenges which have presented themselves. Our membership of the European Industrial Pharmacists Group has given us access to their digital webinars with a view to address the professional development needs of our members.

IN 2017 THE MALTA MEDICINES VERIFICATION ORGANISATION, OR MAMVO, WAS SET UP, TASKED WITH IMPLEMENTING THE FALSIFIED MEDICINES DIRECTIVE – WHICH COME INTO FORCE ON 9 FEBRUARY 2019 - ACROSS THE MALTESE PHARMACEUTICAL NETWORK. YOU REPRESENT MQPA AS ASSOCIATE MEMBER ON ITS BOARD. WHAT IS MAMVO'S ROLE?

The Falsified Medicines Directive (FMD) necessitates that marketing authorisation holders (MAHs) include two safety features on all prescription-only medicines placed on the European market i.e. a unique identifier, in the form of a data matrix with a serialisation number, and an anti-tamper device. The serialisation numbers are uploaded to a European central hub by the MAHs; the hub then transfers this data to all the EU and EEA countries, which have their own national repositories. Thus, the Maltese repository contains the serial numbers of prescription-only medicines intended for the Maltese market. Prior to dispensing, pharmacists need to check the anti-tampering device and scan the data matrix; when the product is dispensed the status of the pack is changed from 'active' to 'supplied'. If a medicine intended for another market e.g. Ireland is placed on the Maltese market via an Article 126a registration or parallel importation, upon scanning, the Maltese respository retrieves that number from the national repository of the other country, via the hub.

MaMVO has been established to implement the provisions of Commission Delegated Regulation (EU) 2016/161, which came into force in 9 February 2019. MaMVO administers the local respository and ensures that all wholesaler dealers and pharmacies are connected to the respository with a view to validate medicines' authenticity. MaMVO is also a coordination centre for investigation of alerts. Some alerts may arise due to an identifiable event e.g. repeated scanning of the same product or from a missing serialisation number which was not uploaded in the European repository due to technical problems. If there is no identifiable cause, the Maltese Medicines Authority needs to be alerted to investigate further since it is the competent authority, identified by the Commission Delegated Regulation, that has the legislative responsibility to do so.

LET US CONSIDER A MALTESE WHOLESALER WHO DISTRIBUTES PRESCRIPTION MEDICINES LOCALLY AND WHICH ARE SOURCED FROM A UK COMPANY WHICH RELEASED THE MEDICINES PRIOR TO 9 FEBRUARY 2019. THIS MEANS THAT THESE MEDICINES WILL BE NON-FMD COMPLIANT, RIGHT?

Not necessarily. Companies may have been producing FMD-compliant packs *prior to* 9 February 2019 and, in this case the serialisation numbers would have been uploaded by the MAHs. However, some packs released prior to 9 February 2019 may have a unique identifier but no anti-tamper device, and these numbers would not have been uploaded. Also some products may have a data matrix for serialisation purposes in another non-EU market, such as India, where the serialisation requirements differ from the EU's FMD requirements. If these packs are scanned, a false alert will be generated.

WHEN DO YOU ENVISAGE THAT ALL PRESCRIPTION-ONLY MEDICINES WILL COMPLY WITH FMD LOCALLY?

There is no legislative deadline for all prescription-only medicines to become compliant, so the easiest computation would be the shelf-life of current stocks. Since the serialisation process can be quite challenging some companies may have resorted to stockpiling prior to the 9 February deadline. I envisage that all prescription-only medicines will probably become compliant within approximately 5 years.

WHAT ARE YOUR THOUGHTS ABOUT BREXIT VIS-A-VIS FMD?

As things stand, if there is a no-deal Brexit, the UK repository should be disconnected from the European hub since there can be no data transfer between the EU and 3rd countries without any overarching agreement and to date there is no such agreement. Efforts are underway to try to prevent the consequences of this but some events are beyond our control … we will have to wait and see.

DO YOU ENVISAGE ANY CHALLENGES IN THE FORTHCOMING YEARS?

In 2020 the industry will experience additional reporting obligations in relation to the *anticipation* of shortages, their envisaged duration and an action plan to manage these shortages. We are also seeing an increased use of biosimilars which require different professional skill sets locally, and not only from a manufacturing perspective; even clinically, biosimilar subsitution is a very different prospect to generic substitution.

DO YOU BELIEVE THAT PARALLEL IMPORTATION SERVES ITS PURPOSE LOCALLY I.E. MAKING MEDICINES LESS EXPENSIVE AND MORE ACCESSIBLE TO PATIENTS?

The traditional expectation is that parallel importation results in lower-priced medicines. Perhaps what has happened locally is that parallel importation has helped make some supply chain actors and healthcare operations more economically stable. This is also beneficial in the provision of primary healthcare.

WE ARE HEARING A LOT ON AI, BLOCKCHAIN & LEDGERS. IS THERE SCOPE FOR AI IN THE PHARMACEUTICAL INDUSTRY LOCALLY?

I have recently been involved in research on olive oil and honey, using chemometrics, which is a field of application of AI. These are natural compounds and therefore by their very nature a mixture of many different compounds. Rather than employing excessive efforts to fully separate the components, we adopted self-learning statistical tools to help in the analysis of these complex molecules. I see these techniques as being transferable to the pharmaceutical industry, with various applications.

The marriage of AI with pharma is an exciting field which still has to bear fruits locally. Returning to the issue of shortages, there are tools which utilise self-learning models for extremely complex operations research analyses to predict under what conditions a shortage might be expected. Similar techniques can also be applied in quality control, but I believe it will also lead to a paradigm shift in quality assurance since if the machine can modify and optimise its response, then output response is continually improving and is not fixed. How do you conduct validation in this case?

> "I AGREE THAT MALTA SHOULD HAVE ITS OWN NOTIFIED BODY BUT THIS WOULD TAKE TIME TO DEVELOP IN VIEW OF THE FACT THAT THERE ARE OTHER OPPORTUNITIES AND CHALLENGES WHICH DEMAND OUR ATTENTION, INCLUDING THE MEDICAL CANNABIS PRODUCTION"

DO YOU SEE ANY DIFFERENCE BETWEEN THE NATIONALIST & LABOUR ADMINISTRATION WITH RESPECT TO YOUR FIELD OF PRACTICE?

Malta Enterprise is entrusted to attract investment in Malta. It was active under the previous administration when it successfully attracted generic pharmaceutical companies to set up their manufacturing operations in Malta. Along the years this playing field has levelled off but Malta Enterprise has managed to identify another budding field i.e. medical cannabis production, and is spearheading this, together with the Medicines Authority. The Authority is also delving into innovative areas such as health technology assessments and medical devices regulation. Thus I think under both administrations, these organisations managed to identify the right opportunities for Malta and implement a successful strategy.

MALTA COULD HAVE ITS OWN NOTIFIED BODY FOR THE REGISTRATION OF MEDICAL DEVICES. THIS WOULD CERTAINLY REPOSITION MALTA ON THE EUROPEAN REGULATORY MAP AND CREATE A NEW INVESTMENT NICHE WITH ALL ITS RAMIFICATIONS. WHAT ARE YOUR THOUGHTS?

Unfortunately there are very few notified bodies in Europe, which is a cause of concern. So yes, I agree that Malta should have its own Notified Body but this would take time to develop in view of the fact that there are other opportunities and challenges which demand our attention, including the medical cannabis production. However, Malta has always managed to punch above its weight through hard work, competence and successful foresight. Hats off to that!

I READ THE SYNAPSE BECAUSE...

I always find at least one article, sometimes more, which is relevant to the need to increase my knowledge and remain abreast of current developments. Its intrinsic value is that it increases the knowledge of its readers. Your eLearning Modules are also a valuable tool in this respect.

DETECTION OF SUBTLE BREAST CANCERS WITH MAMMOGRAPHY

THE IMPORTANCE OF USING THE CORRECT TECHNOLOGY AND TECHNIQUE

DR PIERRE VASSALLO

Mammography is an excellent tool for the detection of breast cancer. Screening mammography has been repeatedly shown to reduce breast cancer mortality by up to 40%.[1] It is also associated with earlier stage diagnoses that require less extensive treatment.

However, screening mammography is not without its caveats. Ten to 30% of cancers can be missed if subtle findings are not detected. Breast cancer must be detected before it causes clinical symptoms, otherwise more treatment is required, and prognosis may be worse.

The main factors contributing to missed cancers on mammography include:[2]

- Dense breasts: dense glandular tissue may obscure a cancer.
- Poor positioning and technique: old technology, incomplete coverage of breast tissue, poor positioning.
- Failure to compare with past mammograms.
- Type of cancer: some cancers grow slowly appearing stable over many years, while some don't cause a desmoplastic reaction.
- Non-perception or incorrect interpretation of findings.

The ways to avoid missing cancers include the following:

- Use of the best imaging technology.
- Meticulous attention to correct technique.

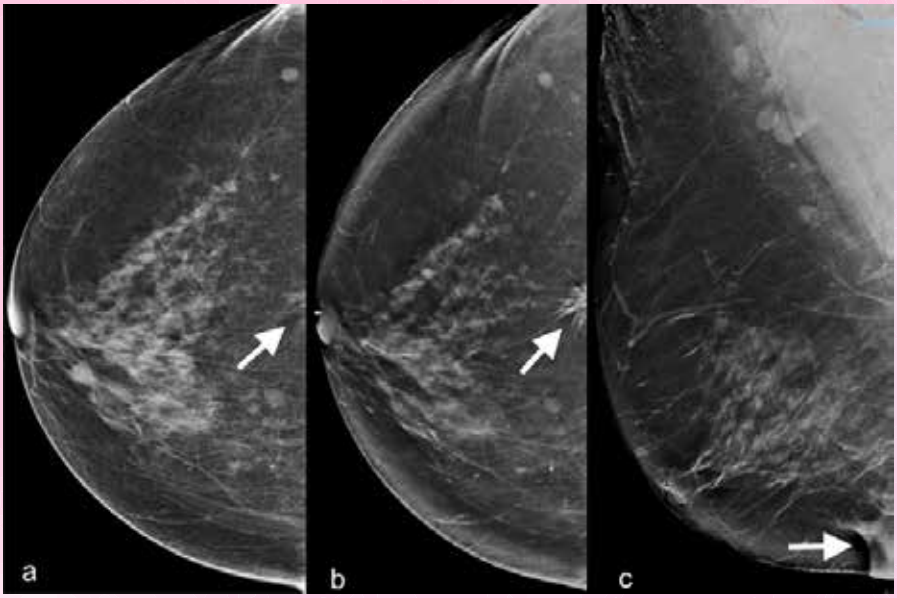

Figure 1. a. CC view showing a near-chest-wall subtle asymmetry (arrow). **b.** CC view one year later showing an obvious spiculated lesion at same location (arrow). **c.** Ultrasound confirmed the lesion to be located at 0600; this is not seen due to incomplete depiction of the inframammary fold (arrow).

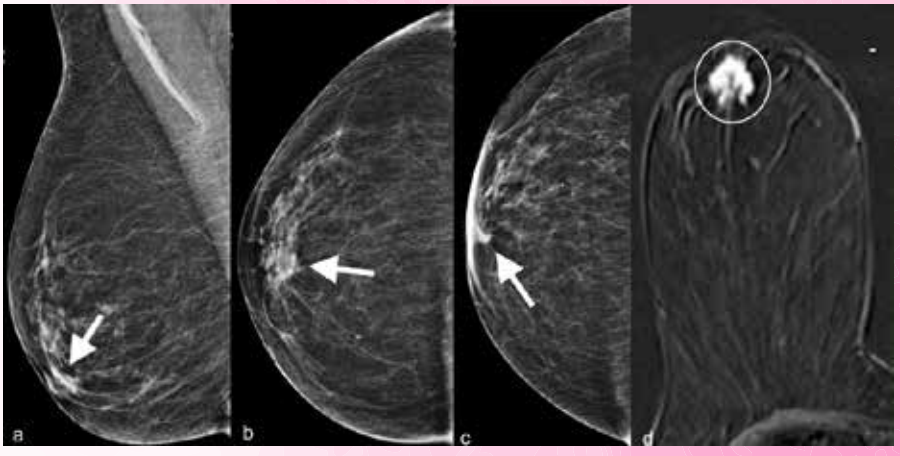

Figure 2. a. MLO and **b.** CC views of right breast do not depict retroareolar cancer (arrows). **c.** CC view with nipple in profile showing a retroareolar cancer (arrow). **d.** Corresponding post-IV-contrast T1-weighted subtraction MR image showing the retroareolar invasive ductal cancer (circle).

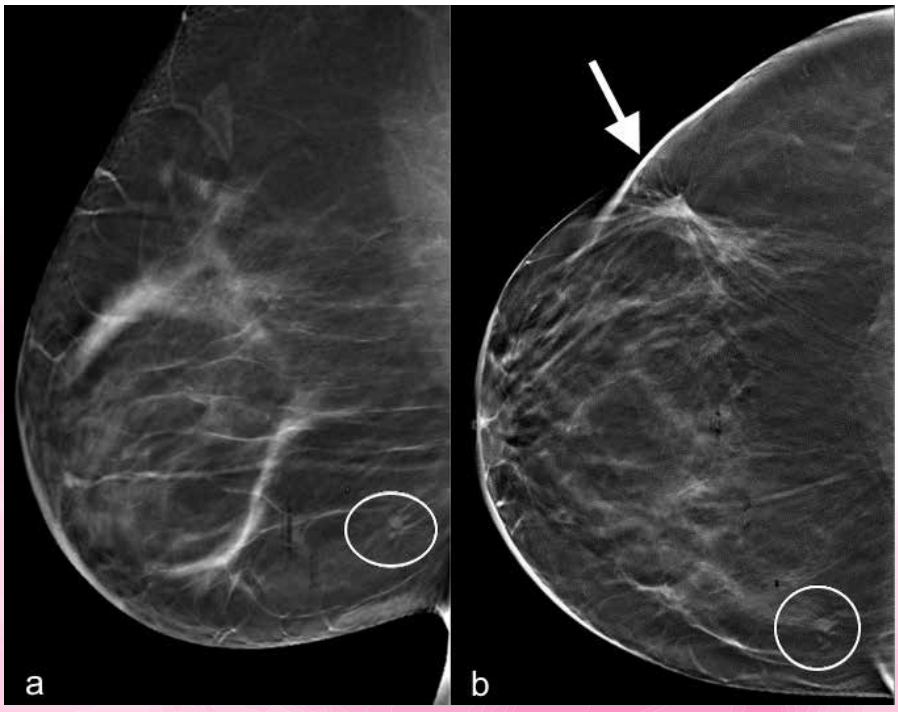

Figure 3. a. Right MLO and b. Right CC images from DBT stack performed on a patient who had a cancer nodule excised (arrow) followed by radiotherapy; both images show a subtle near-chest-wall lower inner quadrant invasive mucinous cancer (circle).

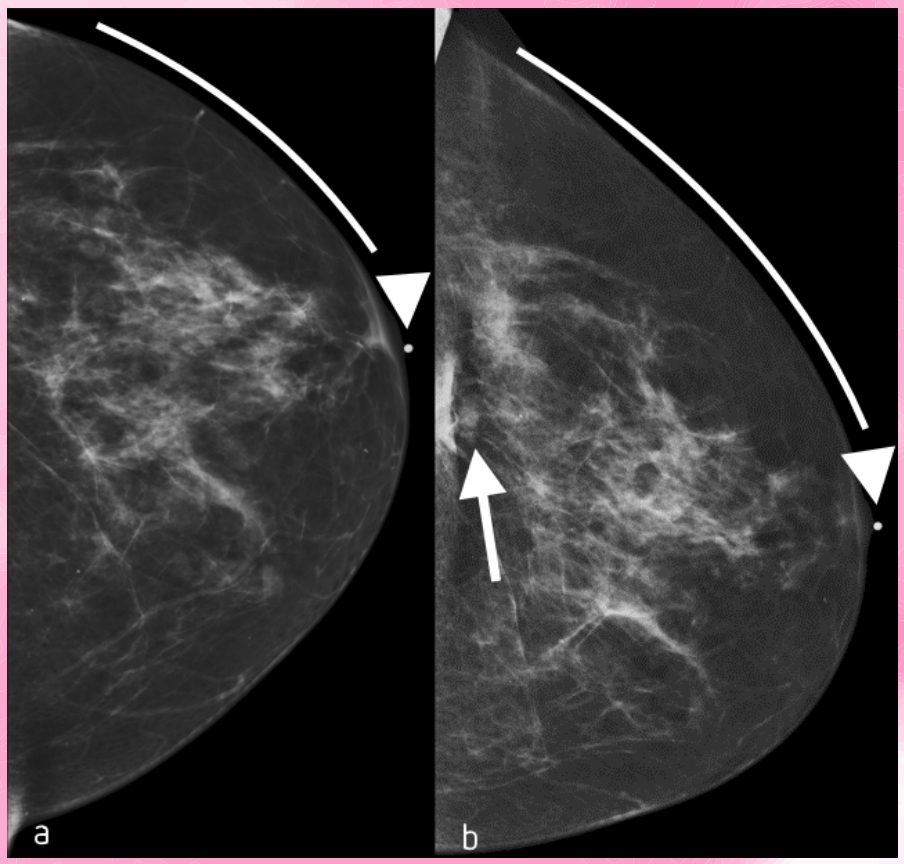

Figure 4. a. Left CC view taken a year earlier with nipple pointing laterally (nipple marker – arrowhead) and incomplete inclusion of the lateral breast (line). **b.** Recent left CC view with nipple in correct central position (nipple marker – arrowhead) that includes the lateral breast tissues (line) and shows a small lesion (arrow) that on biopsy was confirmed to be an invasive ductal cancer.

- Utilisation of standard search patterns.
- Comparison to multiple past images.

There are different types of technology used to obtain mammograms; these reflect mostly different stages of technological development. The type of technology available varies from one imaging department to another. Computed Radiography (CR) mammography has been available for around 25 years and is still used in many institutions today. On the other hand, Direct Digital (DR) mammography delivers superior image quality resulting in significantly improved diagnostic accuracy. DR mammography is considered the gold standard for breast cancer screening.

The last 8–10 years have witnessed a further development in DR mammography, whereby the standard 2D technique was combined with the principle of X-ray Tomography to create 3D mammograms. This technique is known as Digital Breast Tomosynthesis (DBT). Its main advantage is that it addresses the problem of tissue overlap, which is often encountered in dense breasts. It is an excellent tool for analysing equivocal findings particularly in denser areas of the breast. The latest research studies suggest that this will eventually replace 2D mammography as a primary breast cancer screening test.

While CR mammography is still widely available, this method should be avoided for breast cancer screening in favour of DR mammography or DBT, since these modalities are more accurate.

Given the considerable improvements in image quality attained with both DR and DBT technologies, the remaining factors that influence mammography accuracy are mostly examiner-related. These may be related to radiographer technique (patient positioning, avoiding motion artefact and adequate compression) or radiologist analysis and interpretation methods (ensuring all areas of the mammogram are included and analysed, confirming that technique is adequate to allow accurate analysis, and detailed comparison of current with prior mammograms).

RADIOGRAPHER TECHNIQUE

Incorrect positioning may limit the image diagnostic value of a mammogram.[3] To cover all parts of the breast on mammogram, an *up-and-out positioning* technique is used; the breast must be drawn out to include the chest wall muscles and up to include the inferior axillary fold. The difference in distance between the nipple and chest wall muscles on mediolateral oblique (MLO) and cranio-caudal (CC) view must be less than <1cm. Figure 1 shows a near-chest-wall cancer located in the inferior breast fold that is poorly seen in image a. due to incomplete inclusion of posterior tissues but is evident in images b. and c. taken with correct up-and-out positioning.

The *nipple must be displayed in profile* otherwise cancers located just beneath the nipple may be obscured. Figure 2 shows a cancer located deep to the right nipple that is only evident when the nipple is positioned on profile. Further imaging of the nipple area with breast ultrasound or MRI may be required in equivocal cases, however if the nipple is incorrectly positioned on the mammogram, one may not be alerted to that need.

The retroglandular and inferior and medial triangle should only contain fat or muscle. Any density in these areas, especially if new, should be deemed suspicious. Figure 3 shows a subtle cancer in the inferior fold, which may have been overlooked if the inferior fold had not been completely imaged.

There must be *adequate inclusion of lateral and posterior portions of the breast on CC view*. Note the differences between image a and b in Figure 4; a nipple marker identifies the location of the nipple (arrowhead) and the line drawn outside the margin of the breast shows the difference in the amount of lateral breast tissue included in each image. The small cancer located in the posterior fat on image b. is not seen on image a. because of incorrect positioning.

Inadequate compression and patient motion may degrade image quality and obscure cancers. Inadequate compression results in limited beam penetration and increased tissue overlap. Patient motion blurs important signs such as architectural distortion and

[WHEN IMAGING THE AXILLAE] IT IS CRUCIAL TO COMPARE CURRENT WITH PRIOR IMAGES THAT ARE AT LEAST TWO YEARS OLD...

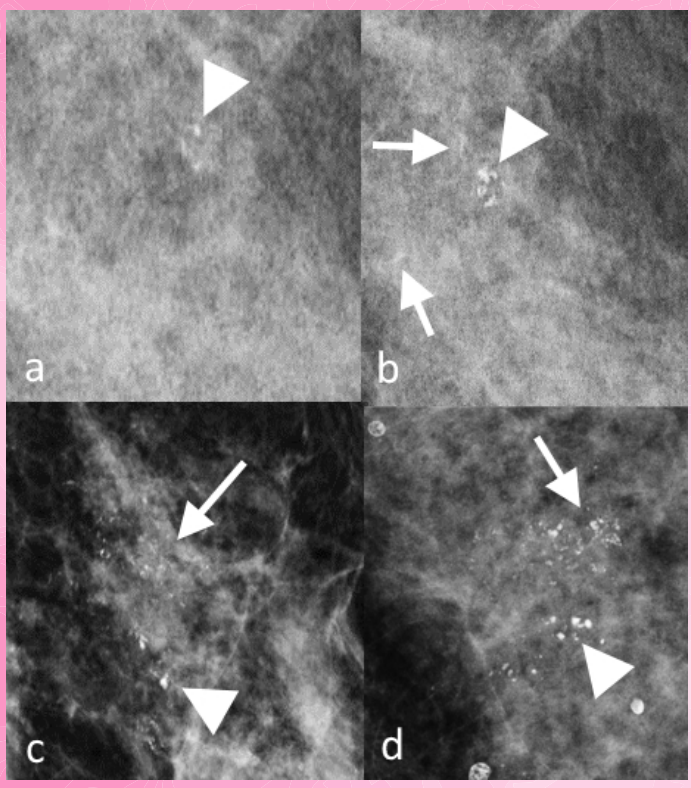

Figure 5 a. and **b.** are two mammograms taken one year apart. a. the initial mammogram, shows scanty coarse calcifications (arrowhead), which in b. appear more coarse and therefore more likely benign. In retrospect, b. shows additional calcifications (arrows). However, there is motion artefact in both mammograms a. and b. Patient motion or respiratory motion can both cause blurring particularly on spot compression/magnification views like a. and b., since longer exposure times are needed. **c.** and **d.** were taken a further year later with adequate compression to prevent motion; both images shows clustered microcalcifications distributed in a linear fashion (arrows), a feature of DCIS (ductal carcinoma in-situ).

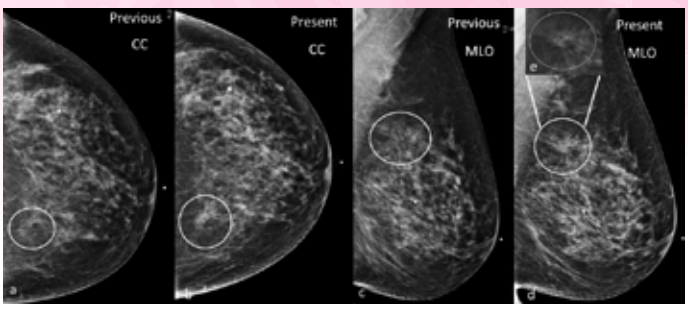

Figure 6 a. and **b.** are CC views and c. and d. MLO views of the left breast taken 1 year apart. They show a subtle developing asymmetry along the posterior fat-glandular margin (circle). Subtle changes in the contour of the fat-margins may be easily overlooked.

microcalcifications. This is particularly true with spot compression and magnification views due to the long exposure times required (Figure 5).

RADIOLOGIST ANALYSIS

Use of a standard search pattern by the radiologist may avoid missing lesions in areas that are often overlooked:

- Anterior and posterior glandular/fat interfaces (Figure 6)
- Retroglandular fat
- Lower and inner triangles
- Edges of images (Figure 7)
- Skin
- Nipple-areolar complex
- Axilla and lower axillary tail

Careful *review of the axillae for new lymph nodes or increased lymph node size* is particularly important in patients with a prior history of excised breast cancer (Figure 8). In addition, it is crucial to *compare current with prior images that are at least two years old* as slow growing cancers may appear unchanged in the short term. Finally, one must give importance to the clinical findings; *any clinically suspicious finding that finds no mammographic correlation should be imaged further with ancillary modalities* such as DBT, ultrasound and MRI and, if still in doubt, with percutaneous biopsy.

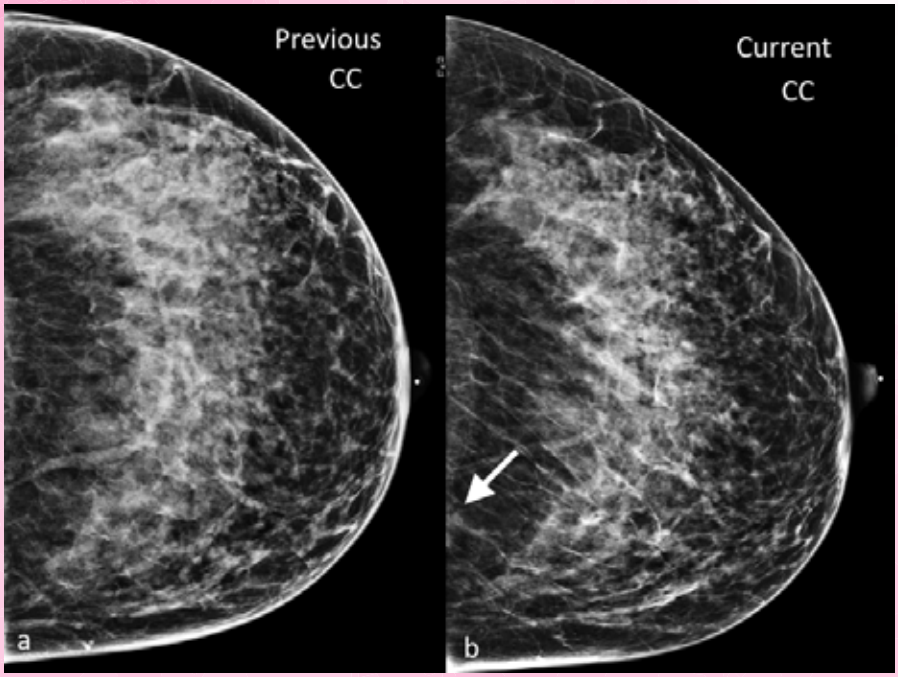

Figure 7. Previous **a.** and current **b.** CC views of the left breast show the importance of examining the edge of the mammograms. The arrow in b. indicates a new asymmetry in the posterior and medial portion of the left breast, which was later confirmed to be an invasive lobular cancer.

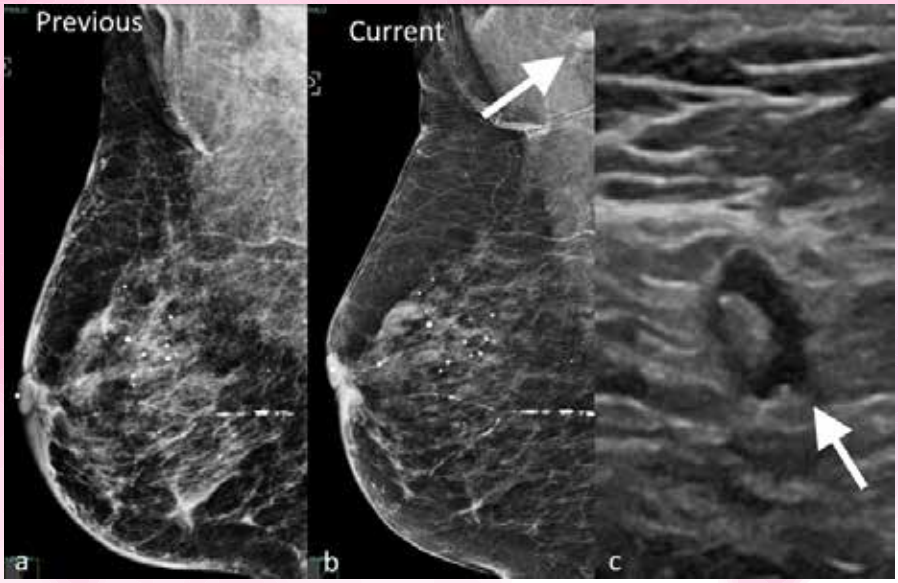

Figure 8. Previous **a.** and current **b.** MLO views of the left breast showing interval development of a left axillary lymph node (arrow). **c.** Ultrasound image of the left axilla confirms the presence of a non-enlarged lymph node with asymmetric cortical thickening and margin irregularity (arrow). Biopsy of the lymph node confirmed metastatic invasive ductal cancer.

CONCLUSION

In summary, the steps that must be considered by any mammography service wanting to improve its diagnostic accuracy are as follows:

Selection of highest quality imaging equipment, which should include DR Mammography and DBT.

Ensure correct positioning in all mammograms (nipple in profile, open inframammary fold, adequate inclusion of retroglandular tissue, <1cm difference in pectoralis nipple distance on CC and MLO views), avoid motion artefacts and ensure adequate compression.

Maintain a standard search pattern (anterior and posterior fat-glandular interface, axillary tail and axilla, retroglandular fat, inner and lower triangles, skin and nipple-areolar complex, check edge of images).

Compare current with previous mammograms that are at least 2 years old (look for developing asymmetries, enlarging lymph nodes, parenchymal distortion and changes at the post-surgical sites).

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Amoxicillin/Clavulanate Potassium

Powder for oral suspension

- Provides extended antibacterial coverage to include the most penicillin-resistant strains.[1]
- Recommended by leading Guidelines as first line treatment in AOM.[2,3]
- Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.[4]
- Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.[4]

Spreading infectious energy!

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

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