THE SYNAPSE

THE MEDICAL PROFESSIONALS' NETWORK

Volume 18, 2019 Issue 06 ISSN number 2313-8084

Meeting Dr Joseph Debono

Life After a Cardiac Event

An AI with Empathy?

Clinical Translation of Stem Cell Research

Imaging Cancer of the Rectum

DUAC (CLINDAMYCIN/BENZOYL PEROXIDE) IS AN EFFECTIVE TREATMENT THAT HELPS YOUR MILD TO MODERATE ACNE PATIENTS TO SEE IMPROVEMENTS FAST[1,3]

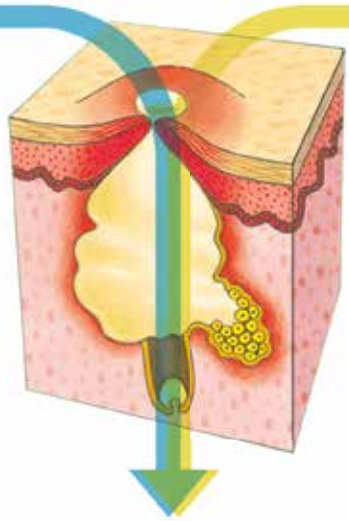
DUAC HAS A DUAL MODE OF ACTION[2]

Benzoyl Peroxide

- Keratolytic[2]
- Treats comedones[2] and inflammatory lesions[5]
- Bactericidal action against *P. acnes* strains[2]

Clindamycin

- Suppresses *P. acnes* [2]
- Anti-inflammatory action[5]



Duac:[2]
Unblocks follicles
Reduces inflammation
Kills bacteria
Reduces the potential for bacterial resistance

DUAC UNDERSTANDS WHAT'S IMPORTANT TO PATIENTS

- **Duac works fast, starting to work in just 2 weeks[3]**
- **Duac is a once daily treatment[2]**
- **Duac is generally well-tolerated[2,5]**

Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[1]

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[4]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin

• Gently pat dry

• Apply a thin layer of Duac gel on the affected area, not just the individual spots

TIPS[4]

If your patient's skin peels or becomes dry, they can try:
- Using an oil and fragrance-free hypoallergenic moisturiser
- Using Duac less often, or stopping for one or two days before starting again

DUAC ONCE DAILY GEL 10mg/g + 50mg/g ABRIDGED PRESCRIBING INFORMATION

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

TRADE NAME: Duac Once Daily Gel 10mg/g + 50mg/g. **ACTIVE INGREDIENTS:** Clindamycin phosphate/anhydrous benzoyl peroxide. **PHARMACEUTICAL FORM:** Gel. **INDICATIONS:** Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. **POSOLOGY:** Adults and Adolescents (12 years and over): Once daily (evening) to affected area. Should not exceed more than 12 weeks. Applied in a thin film after washing gently with mild cleanser and fully drying. Was hands after application. **CONTRAINDICATIONS:** Hypersensitivity to active substances/lincomycin/excipients. **PRECAUTIONS:** Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated/broken skin. Caution in patients with a history of regional enteritis, ulcerative colitis, antibiotic-associated colitis, atopic patients, concomitant topical acne therapy. Increase in peeling and reddening will occur in most patients during first few weeks of treatment. If severe local irritancy, discontinue. Prolonged exposure to sun should be avoided. In patients with sunburn, this should be resolved before use. If significant diarrhoea/abdominal cramps occur, discontinue (symptoms may indicate antibiotic-associated colitis). May bleach hair or coloured fabrics. Patients with a recent history of systemic or topical clindaymcin and erythromycin are more likely to have pre-existing anti-microbial resistant Propionibacterium acnes and commensal flora. Cross-resistance: May occur when using antibiotic monotherapy. **PREGNANCY /FERTILITY / LACTATION:** *Pregnancy:* only after careful risk/benefit assessment. *Fertility:* no data. Lactation: should not be applied to breast area. **UNDESIRABLE EFFECTS:** Very common (≥1/10): erythema, peeling, dryness. Common (≥1/100 & <1/10): burning sensation. Refer to the SPC for full list of undesirable effects. **LOCAL PRESENTATION:** 30g gel. **MARKETING AUTHORISATION NUMBER:** MA192/02801. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline (Ireland) Ltd. Legal Category: POM. **Date of Preparation:** May 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).

REPORTING ADVERSE EVENTS (AEs):

Suspected adverse events should be reported to GSK Malta through: gskpro.com/en-mt (Phone: +356212381311, Address: GSK Malta, 1 (1st floor), de la Cruz Avenue, Qormi, Malta). Malta: Cases may also be reported through medicinesauthority.gov.mt/adrportal (Malta Medicines Authority)

References: 1. Langner A *et al.* BJD 2008; **158**: 122–129. **2.** Duac 5% Summary of Product Characteristics March 2019. **3.** Langner A *et al.* JEADV 2007; **21**: 311-319. **4.** Duac 5% Patient Information Leaflet, March 2019. **5.** Lookingbill DP *et al.* JAAD 1997; **37**: 590-595.

Stiefel
a GSK company

For more information
https://gskpro.com/en-mt/products/duac/

Duac once daily gel
Clindamycin 1% and benzoyl peroxide 5%

Job no.: PM-MT-CBP-ADVR-19001 Date of preparation: November 2019

ROCKING THE BOAT

In our last editorial the Junior Minister for Financial Services, Digital Economy and Innovation within the OPM, Silvio Schembri, discussed the transformation of healthcare through AI. Indeed, the percolation of AI and machine learning technologies in healthcare may effectively translate in a cornucopia of applications. AI certainly has a role in the prediction of pharmaceutical properties of molecular compounds as well as the identification of disease-modifying targets. In previous editorials we have also discussed at length how AI can improving diagnostic accuracy in clinical practice whilst reducing the time needed to achieve such diagnosis. This results in improved patient outcomes and, on a societal level, a decrease in costs of care. In keeping with this, recently the Deputy Prime Minister and Minister for Health, Chris Fearne stated that in 2020 Malta will be introducing a monitoring system for children with diabetes … operated with AI.

However, AI has other useful applications. In our interview with Dr Joseph Debono (page 6) we discuss the need for additional ward space and recovery beds at Mater Dei hospital. Here, AI-powered predictive analytics can be used to optimise bed management by scrutinizing both historical and real-time patient admittance rates, while also analysing staff performance in real time. Another overlooked aspect of AI is its role in caregiving, including end-of-life care. Ageing makes us face various realities, be it dementia, loneliness or limited mobility. AI may revolutionise caregiving through the use of chatboxes and affective computing by providing conversations and other social interactions to keep aging minds healthy. On page 9 we have an interesting article on affective computing by Luca Bondin & Prof. Alexiei Dingli.

The Synapse is in the process of launching a new portal offering online CPD for doctors providing single educational sessions, online courses and masterclasses which can be conveniently done anywhere, as long as there is an internet connection, even on smart phones. In this respect e-Learning will only stand to benefit from AI-driven infrastructure; machine-learning algorithms will hone on the user's knowledge and understanding of the training material and present them with relevant content more quickly.

However, the medicalisation of AI heralds a plethora of challenges, including ethical conundrums relating to the acquisition of sensitive health data and their protection. The following are important considerations. The acquisition of patients' data for use in machine-learning algorithms requires consent by patients for such use? Is re-consent needed if data are used for different algorithms? How does one validate the models which are made, and gauge their risk? If algorithms are not patent protected, will industry advocate intellectual property to circumvent audits? And will patients need to consent if their care is affected by the use of these algorithms? An in-depth analysis of each of these areas needs to be conducted.

A future editorial will discuss bias, as well as medical malpractice and product liability which may arise, especially with the use of black-boxes and unsupervised algorithms. Until we meet again, I wish you and your loved ones a New Year filled with happiness and good health!

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The magazine is distributed free of charge to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies.

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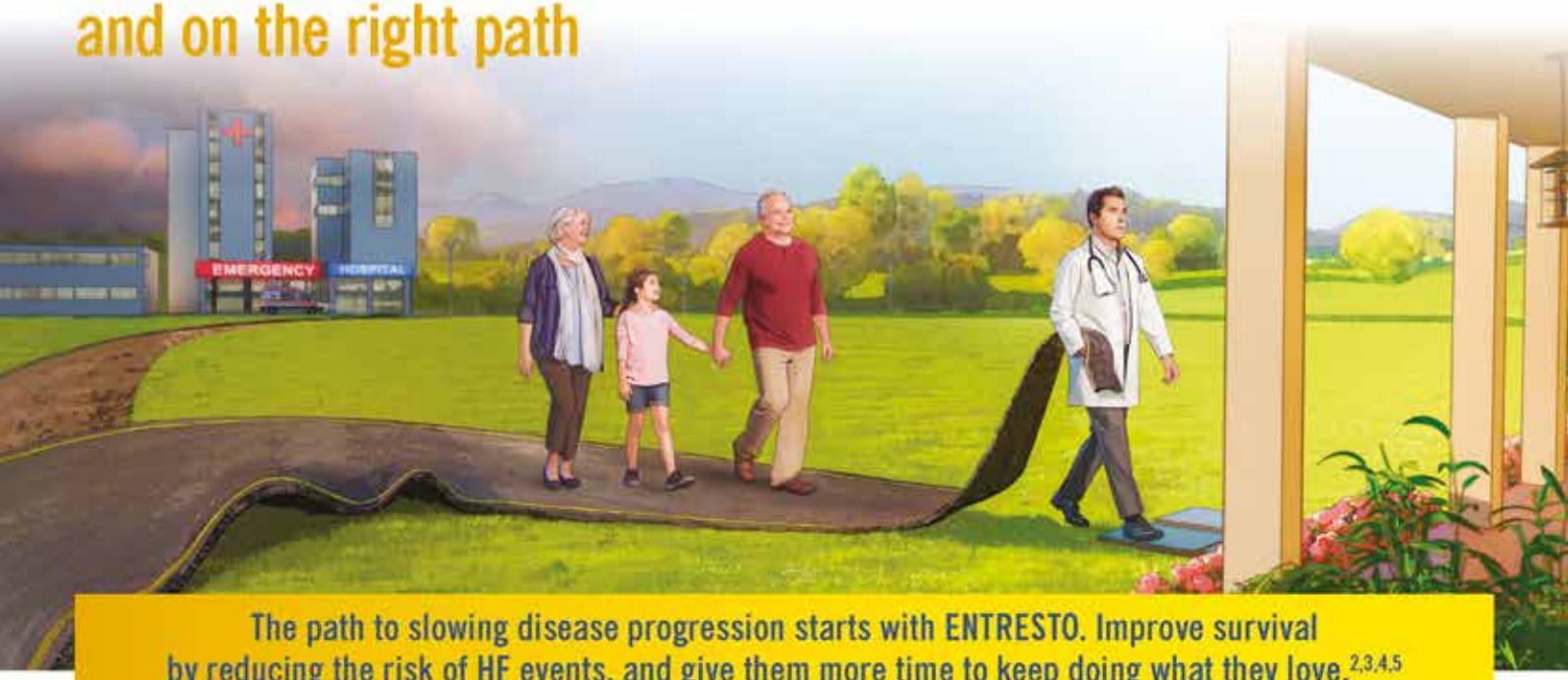
Keep HFrEF patients alive, out of the hospital, and on the right path

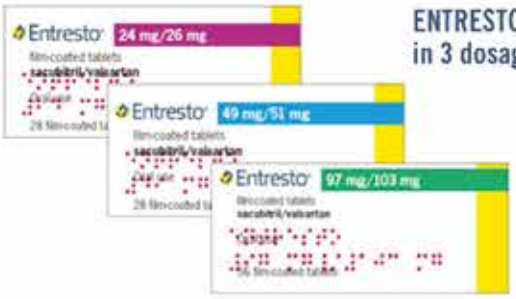


The path to slowing disease progression starts with ENTRESTO. Improve survival by reducing the risk of HF events, and give them more time to keep doing what they love.[2,3,4,5]

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.

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Entresto®
sacubitril/valsartan

AUTHORS

Dr Alfred Grech MD graduated from the University of Malta in 1985. He has been working in Primary Health for these last 30 years. His special interests are molecular biology and epigenetics. As a pastime he cultivates bonsai trees and plays his sax alto. The co-authors of the article are Dr Stephen West & Dr Ramon Tonna.

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ISSUE GUIDE

TheSynapse

LIFE AFTER A CARDIAC EVENT

Dr Ian Ellul chats to DR JOSEPH DEBONO – distinguished surgeon – over a cup of coffee in his office at Mater Dei Hospital.

YOU GRADUATED AS DOCTOR IN 1988, STARTED YOUR SURGERY TRAINING IN 1990 AND BECAME FULLY SPECIALIZED IN 1999. BUT LET US GO FURTHER BACK IN TIME. WHAT MEMORIES DO YOU HAVE OF YOUR CHILDHOOD AND ADOLESCENCE?

We were a very close-knit family. Both parents worked and I still have fond memories of myself and my two siblings negotiating the division of household chores. We used to eat healthily but unfortunately, did not exercise. In this respect, the fact that I was an avid reader did not help much.

When my father was 45 years of age he had to undergo bypass surgery. This was a watershed moment for all the family. I was at University at the time. My father was always very active, fitting a myriad of activities in his free time – he was also a carnival float-maker – but within a few hours, his life had to change drastically.

At 24 years I got married and had my first child 18 months later. It was a very hectic period since we had to relocate to Scotland for my specialisation. This 7-year stint meant long hours working 1 in 2's and 1 in 3's with exams in between. It was practically work, study & family. After returning to Malta I embarked on a busy career. Then in a blink of an eye I reached the age of 45 years when my father had his cardiovascular event. This moved me to seriously reconsider my health. As I was deliberating, my wife decided to do the half-marathon after an inactive life. When I saw her cross the finish line with great satisfaction on her face, I remember thinking to myself … if she can do it, so can I! At this stage I must admit that she was very supportive. She introduced me to her gym – I am still a member there – and encouraged me to embark on a healthy lifestyle. Seven years later, at 52 years of age, I am still dedicated to my goals as ever.

WHY DID YOU CHOOSE MEDICINE & SURGERY?

Since I was young I was always awed by the fact that doctors would do something which made people feel better, so it was only natural for me to become one. However, when it comes to specialisation, it is really an interplay of events which leads to this … preference of one speciality over another during the years of rotation, the timing of the publication of the vacancies, personal circumstances like the cardiovascular event of my father, etc. At first I wanted to go into medicine, then pediatrics, then pediatric surgery and then finally surgical oncology. So there you are ... no regrets at all.

DO YOU HAVE ANY MEDICAL ANECDOTES TO TELL?

Plenty, like when patients are convinced (and try to convince me) that plant extracts can cure them of breast cancer. However, at times such an ordeal can make things turn around. In what can be considered as a sad anecdote, on more than one occasion I have seen women, even elderly ones, who were victims of domestic violence, take the reins of their life in their hands after remission and decide to leave their partners. Surviving cancer can be very empowering.

WHAT ARE TODAY'S CHALLENGES IN SURGERY?

One of the challenges is the limited number of patients in view of the fact that Malta has a small population. I enjoy performing laparoscopic and pancreatic surgery but having the numbers to build and maintain the skill is difficult. Locally it is challenging to have subspecialists. However, having said this, one also needs to gauge whether a surgeon working exclusively as a subspecialist is better off. Revenue apart (which one also must consider) what would be the surgeon's quality of life? … imagine seeing only breast cancer cases day in day out. Also, how could one manage to operate all of those cases in a timely manner and deliver the standard quality of care to each patient? These are all important considerations for every doctor out there pondering on a subspecialisation.

Another challenge is technology. We are now seeing the advent of robotics in surgery which means that skills have to follow suit. Many of us 'older' surgeons have experienced video

games when we were young and this has been shown to translate when using robots in clinical practice. However, after robotics, we will eventually see something else, which means that we would need to re-define our skill set.

We are also living longer with multiple co-morbidities. Surgeons are seeing numerous octagerians and even nonagerians with tumours. Let us consider a 90-year old patient who goes to a private clinic for a FOB test; this comes positive and is then referred for a colonoscopy. Her PMH includes heart failure and is on warfarin. After one discusses with the patient the specific risks which are involved, a colonoscopy is carried out. If one finds something sinister, what then? When should one stop investigating or operating? These are gargantuan ethical dilemmas which surgeons are facing nowadays.

I SUPPORT HEALTHY COMPETITION BECAUSE THIS DRIVES THINGS FORWARD, SIMILAR TO SPORTS, AND BRINGS AN IMPROVEMENT OF SERVICES. HOWEVER, ONE MEDICAL SCHOOL SHOULD NOT HAVE AN IMPROVED SERVICE AT THE EXPENSE OF THE OTHER.

IN OCTOBER THE BARTS MEDICAL SCHOOL OPENED ITS GOZO CAMPUS. WHAT ARE YOUR VIEWS ON THIS?

I support healthy competition because this drives things forward, similar to sports, and brings an improvement of services. However, one medical school should not have an improved service at the expense of the other. Let me bring a practical example. If one's teaching ward round at Mater Dei hospital involves five students [these have decreased], one should not make them ten so that one has more time for the other medical school; rather, one should invest more time and effort in Malta's medical school so that this becomes more competitive.

WHAT ARE YOUR VIEWS ON THE OPERATION WAITING LISTS IN MALTA? DO YOU THINK THE GOVERNMENT IS DOING ENOUGH ON THE MATTER?

The main challenge relates to infrastructure and administration. Although we have theatres, operating time and surgeons, we are in dire need of ward space, recovery space, nursing staff and clerical support to match the needs of the increase in operations.

AT ONE STAGE YOU WERE OBESE. WHAT HAPPENED?

I used to weigh close to 100kg. I started to exercise and eat wisely, every 2-3 hours. The quantity and quality of the food is also important. A person should eat until he is satisified, not until he is full. If one is committed to loosing weight, it is not difficult to achieve this.

YOU WERE A BRAND AMBASSADOR FOR A LOCAL SPORTS RETAIL COMPANY. WHY DO YOU FEEL THE NEED TO CHAMPION SPORTS?

I feel the need to do this from the unhealthiness I see around me on a daily basis, both as a person and as surgeon. Obesity creates so many health problems and surgical complications. Returning to your question, I champion sports because I believe I can be a role model and people take heed of me.

SOME WEEKS AGO YOU SUFFERED A MI. HOW DID IT HAPPEN?

Eighteen August. That was the eventful date. Two days before I ran 17km with no symptoms. However, before that, I had noticed that if my heart beat increased to more than 150 beats per minute, I felt unwell. No chest pain was ever involved. In hindsight I ought to have heeded my body and did some investigations but I blamed the increasing age and the fatigue which stemmed from the fact that I was training 2-3 hours a day in preparation for the Spartan and Ironman events.

On 17 August I did 40km with the bicycle but had to curtail it as I fell off the bike. Again I blamed the heat, fatigue, etc. The day after, on the 18 August, during lunch I started to get chest pains radiating to my shoulder and neck. Despite these textbook symptoms, gross denial kicked in. Eventually my wife drove me to Mater Dei hospital. Investigations showed that I had elevated troponins with no ST segment changes. On 19 August I had my PCI and the rest is history. Currently I am undergoing rehabilitation but am a firm believer that with patience and some readjustment of goals, I will start doing my beloved triathlons again. However, truth be told, I currently do not know where I stand.

WHAT ARE YOUR AFTERTHOUGHTS?

My family history was my only risk factor. Two years ago I did a stress test and it was fine. I do not have cholesterol, no diabetes, do not smoke and have had seven years of healthy living. However, the years before that were not healthy.

WHAT ADVICE WOULD YOU GIVE TO NEWLY GRADUATED DOCTORS AND SURGEONS?

I would recommend that they are true to themselves. One should have a professional behaviour towards one self, colleagues and patients. Some doctors choose this profession for money this is truth, but this only provides temporary satisfaction. It is using your talents, the engagement with patients and seeing them get better that is most rewarding.

My cardiac event was possibly triggered by the fact that I was verging on a burnout. I had too much on my plate ... physical training, work, family. At times doctors are the last persons to seek help for themselves.This should not be the case.

I READ THE SYNAPSE BECAUSE...

It provides an insight on local research which is occurring outside one's practice. One thing which is cherished at Mater Dei but is detested in private practice is loneliness. The Synapse helps you to overcome this by making you feel part of the local medical community in its widest sense.

Helping people with MDD* rediscover the love for life

Bupropion has a lower incidence of sexual side-effects compared with the other SSRIs in MDD* patients^, 1, 2

Wellbutrin XR should not be used together with other Bupropion containing medicinal products.[3]
Wellbutrin XR tablets should be swallowed whole and not crushed or chewed.[3]

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. 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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. 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Job No: PM-MT-BPR-ADVR-190001
Prepared: April 2019

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* MDD: Major Depressive Disorder; SSRI: selective serotonin reuptake inhibitor
^ SSRIs: sertraline, citalopram, escitalopram, paroxetine and fluoxetine
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AN AI WITH EMPATHY?

LUCA BONDIN AND PROF. ALEXIEI DINGLI

Welcome to the 4th instalment of this series discussing AI in the field of health care. We have looked at how we are using AI to help carry out administration work in hospitals, for example, or to help professionals in analysing medical images. We have also looked at the introduction of Virtual Reality as a tool to help both caregivers and care receivers alike. In this article, we would like to introduce another concept related to AI that promises to help further provide added-value healthcare to patients. This concept is called Affective Computing.

Affective Computing was formally introduced to the world in 1997 by Rosalind Picard, Professor of Media Arts and Sciences at the Massachusetts Institute of Technology.[1] In the field of AI, the main goal has always been that of having machines perform human-like tasks, and to a certain extent, the area of AI has gone a long way in achieving this. However, most of the AI already implemented lacks one fundamental human ability: the ability to detect, and understand human emotion. More importantly, most of the existing AI cannot change its behaviour according to human behaviour. If we can make that missing step in giving our machines the ultimate human-like ability, and find suitable applications for it in the area of healthcare, then Affective Computing promises to be a real game-changer.

Researchers have already started looking at how and where to introduce Affective Computing for patient care. A significant part of the world's population is affected by depression, stress and anxiety-related disorders, which are interdependent and directly connected to emotion.[2] Affective systems have successfully been used in mental health interventions or as diagnostic and treatment tools for depression and numerous anxiety-related disorders. Let us give an example. In previous articles, we discussed the adoption of chatbots to help patients with various conditions. What if these chatbots could understand how the patient is feeling while conducting the conversation? What if the AI could detect if a person is showing signs of depression and change its behaviour accordingly to ease the problem before alerting the competent professionals?

Having presented the concept of Affective Computing, we would like to introduce Morpheus. Morpheus is a project undertaken by researchers at the University of Malta that brings together the various concepts we have discussed in this series, from AI to Virtual Reality to Affective Computing. Morpheus, a project funded by the Vodafone Foundation, is about helping young children receiving chemotherapy treatment through distraction therapy. Pain associated with chemotherapy is reduced by analgesics, which can however have adverse effects such as drowsiness, constipation and other gastrointestinal distress. Morpheus promises to provide a safe and effective method of reducing the pain associated with chemotherapy. Through the use of a virtual reality game, we aim to distract children during chemotherapy to reduce the pain which patients experience. Previous articles highlighted the work being carried out by KindVR in the area. However, through the introduction of Affective Computing, we are promising to provide something completely innovative. The virtual reality game will collect physiological data from the child playing the game. It will adapt its experience in real-time to keep the player engaged with what is happening inside the game. The more the patient is involved with the game, the fewer pain symptoms are recorded by receptors in the brain, making the overall experience better.

We are currently on course to complete the first of three iterations of Morpheus and the initial results are indeed promising. We are confident that the approach we are taking will in turn return positive results when the game is eventually deployed for use in hospital wards locally. The introduction of Affective Computing has afforded us the opportunity to make AI something that humans can truly relate with, and its application in the area of healthcare provides researchers, professionals, and patients with opportunities few could have imagined possible a couple of years back.

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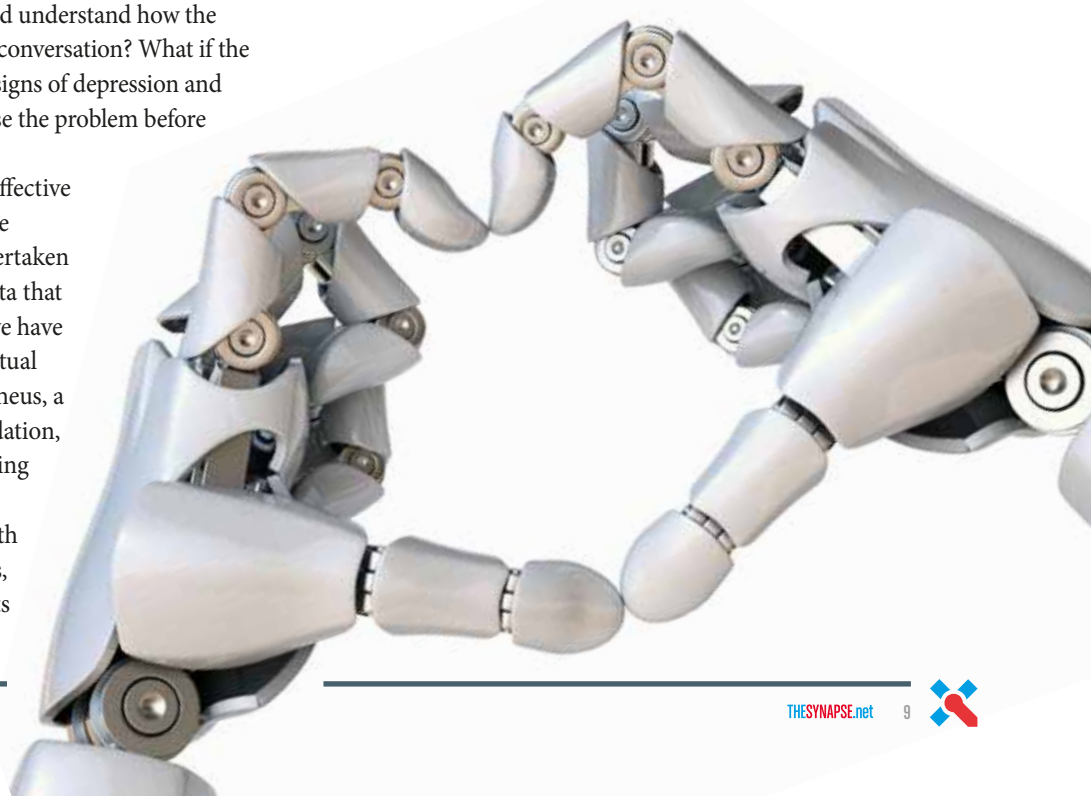

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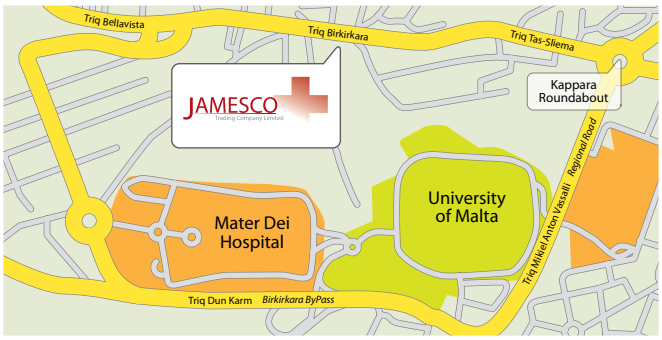

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ANGEL DUST

DR MICHELLE MUSCAT

Angel dust or phencyclidine (PCP)[1-3] is a crystalline powder which can have a high potential for toxicity.[4] This arylcyclohexylamine is usually smoked but can also be taken by other routes such as the intranasal route or injected since it can be dissolved in a solvent. Marijuana can also be laced with PCP.

In the 1950s this drug was marketed as an anaesthetic pharmaceutical but this was later discontinued due to its adverse effect profile. PCP may induce hallucinations, erratic and violent behavior, dissociative states and paranoia. Other psychiatric manifestations have been reported[5] including psychosis and suicidal urges. Other effects include gait disturbance, incoherent slurred speech, balance disturbances, with severe intoxication potentially even leading to convulsions.[6] Instances of self-mutilation, cannibalism, rape and drowning in a bath have been reported to have occurred under the influence. It is neurotoxic and high dosages can give rise to rhabdomyolysis. There is the propensity for drug tolerance and withdrawal. Using dogs as animal models has shown that PCP can cause spasm of the cerebral arteries.[7] Use of angel dust may also have adverse effects on the fetus.

PCP effects are mostly mediated through N-methyl-D-aspartate (NMDA) receptor blockade.[8,9] Research on rodent models have indicated that PCP, being a nicotinic acetylcholine receptor inhibitor,[10] exerts its effect on dopamine receptor binding.[11,12] Other associations include monoamine dysfunction[13,14] and dopaminergic dysregulation.[15,16]

Strategies are sought to deter drug users through education, awareness and drug testing amongst others.[17-20] Further strategies are pursued to prevent abuse. In Malta, organizations and agencies such as Sedqa, Oasi Foundation, Caritas and Narcotics Anonymous provide support for drug-related issues.

As Vourakis and Bennett conclude, angel dust was definitely not heaven sent![21]

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DR ALFRED GRECH,
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CLINICAL TRANSLATION OF STEM CELL RESEARCH

ABSTRACT

Stem cells can be totipotent, pluripotent or multipotent and they can be sourced from various parts of the body. Stems cell research is in hyperdrive and this is responsible for its implementation into the clinical setting. Indeed, stem cell-based therapy has been applied successfully in cancer, hematopoietic and metabolic disorders. But stem cell therapy also has other potential indications in neurodegenerative diseases, stroke, cardiac infarction, arthritis, diabetes mellitus and hearing loss.

INTRODUCTION

HISTORY

Stem cell research started in mid-1800's. The early 1900's saw the discovery of how blood cells could be generated from other cells. It was Alexander Maksimov, a Russian histologist, who in 1908 proposed the term 'stem cell'. In 1968, a bone marrow transplant treated Severe Combined Immunodeficiency with success whilst in 1978 haemopoietic stem cells were isolated from human cord blood. The first human embryonic stem cell line was made by James Thomson and co-workers in 1998.[1] Embryonic-like stem cells derived from blood of the umbilical cord were discovered in 2005[2] and in 2007, stem cells were isolated from amniotic fluid.[3] In 2008, autologous adult mesenchymal stem cells were used to regenerate cartilage in the human knee.[4] In 2009 induced pluripotent stem cells (iPSCs) were derived from skin cells.[5]

DEFINITION

Most multicellular organisms have stem cells. Stem cells are non-specialized, basic cells which have the potency to differentiate into the wide range of adult cells.[6] Beside their ability to differentiate into multiple cell lineages, another characteristic is that they are able to renew themselves mitotically. Importantly, they function in organismal development, growth, maintenance and repair. These functions are being vigorously studied and researched. Indeed, stem cell research is in hyperdrive and promises to offer new revolutionary therapies for various diseases and injuries.

As pointed out, stem cells are unspecialized or undifferentiated. When they become specialized to a specific cell lineage they are differentiated. The process of differentiation is still being studied but it is known that for a cell to become differentiated it must receive signals both from its inside and its outside environment. The internal cues are orchestrated by the cell's genes, whilst the external signals include physical contact and chemical cues like bioactive molecules secreted by other cells in the surrounding micro-environment. These signals interrelate to cause epigenetic changes to the stem cell's DNA thus switching on and off genes which cause the structural and functional changes responsible for the specialization or differentiation of the stem cell.

POTENCY TYPES

A stem cell can be:

- **Totipotent** i.e. capable to give rise to all types of differentiated cells, including the supporting extra-embryonic structures of the placenta.
- **Pluripotent** i.e capable to give rise to all cell lineages of all the tissues of an organism, but not the placenta e.g. embryonic stem cells[7] and iPSCs.
- **Multipotent** i.e capable of forming a range of different cell lineage.
- **Unipotent** i.e capable of generating only one type of specialised cell lineage.

VARIETY OF STEM CELLS

An easy way to classify stem cells is to divide them into early stem cells and adult stem cells. Early stem cells, also called embryonic stem cells, are isolated from the inner cell mass of a blastocyst. Adult stem cells, also called mature stem cells, are found in various body tissues, placenta and the umbilical cord.

APPLICATIONS IN THE CLINICAL SETTING

Stem cells have anti-inflammatory, antifibrotic, antimicrobial, and regenerative capabilities and thus offer the innovative possibility to be utilized to treat damaged tissues and inflammation.

HEMATOPOIETIC DISORDERS

Autologous haemopoietic stem cells (HSCs) have been used for many years to treat malignant blood diseases like lymphomas and myelomas. However, HSCs when used alone may cause adverse rejection reactions like graft versus host disease and bleeding.[8] In clinical trials, it was found that adding mesenchymal stem cells (MSCs) can help prevent rejection. This is because MSCs have immune-suppressive properties. Another asset is that MSCs secrete cytokines that help haematopoiesis and thus aid in bone marrow recovery.[8,9]

LUNG DISEASES

MSCs are also showing great potential in the treatment of chronic lung diseases such as idiopathic pulmonary fibrosis (IPF), obstructive bronchiolitis[6] and chronic obstructive pulmonary disease (COPD). Several studies on various animal models of these diseases have shown that MSCs have protective and reparative effects and these acted as platforms to go into clinical trials. Indeed, several clinical trials are ongoing with encouraging early results.

Clinical trial with ClinicalTrials.gov Identifier: NCT02216630 is a multi-center study using stem cells from adipose tissue and then delivered intravenously to patients with COPD. Here the stem cells obtained via liposuction are not manipulated and not cultured. ClinicalTrials.gov Identifier: NCT02161744, ClinicalTrials.gov Identifier: NCT02161744, ClinicalTrials.gov Identifier: NCT02645305, and ClinicalTrials.gov Identifier: NCT01110252 are some other clinical trials on COPD patients.

Some clinical trials on IPF include those with ClinicalTrials.gov Identifier: NCT01919827, ClinicalTrials.gov Identifier: NCT02013700, and ClinicalTrials.gov Identifier: NCT01385644. Research is also entering the asthma arena. Already in 2019 Zhong et al.[10] have shown that human iPSC-MSCs given systematically protect mice from airway inflammation associated with chronic allergies and thus averting fibrosis. Moreover, a possible pathway mechanism (the TGF-β1/Smad pathway) was identified of how the stem cells might have worked. Clinical trial with ClinicalTrials.gov Identifier: NCT03137199 is a phase 1 investigation on 6 participants using allogeneic MSCs derived from their bone marrow and then given via an intravenous infusion. The estimated completion date of the trial is May 2021.

CANCER

An important revelation was that MSCs home towards tumour sites. This has led to cancer cyto-therapy, whereby allogeneic MSC are used to target the tumour by deregulating the tumour microenvironment. Naïve (unmodified) and genetically modified MSC (GM-MSC) are being tested. The latter are used to deliver anti-tumorigenic molecules, but successful results are inconsistent and variable.[11]

In a study in mice, in 2018, Kooreman et al.[12] showed that iPSCs can be employed in cancer vaccines to bring about anti-tumour immunity reactions. Indeed, they proposed to use these cells for various types of cancer, prophylactically and also therapeutically. Besides, they showed that this iPSC-based cancer vaccine can be personalised. Interestingly, in April 2019, Leaps by Bayer, the investment arm of the global life sciences company Bayer, and Khloris Biosciences, a biotechnology company have joined forces to develop these novel anti-cancer iPSCs-based vaccines, which potentially can prevent and cure cancer.

Research is also studying stem cell states in various cancer types. It is known that certain molecular dependencies occur in cancer stem cells, which are responsible for the cancer to form and progress and also to be resistant to therapy. Knowing these molecular dependencies could be an avenue in cancer treatment Lytle et al. (2019)[13] studied the stem cell state of pancreatic adenocarcinoma. They found an upregulation of RORy (retinoic-acid-receptor-related orphan receptor gamma) which steer inflammation and the differentiation of T cells. Inhibiting it caused marked decrease in growth of the cancer which lead to improved survival. Thus they are proposing the use of autoimmune drugs as a new strategic treatment.

Another avenue of using stem cells is seen in the phase I clinical trial involving 53 participants who had a recurrence of their high-grade glioma. The trial started in March 2016 and is estimated to finish in June 2020. Its ClinicalTrials.gov Identifier is NCT02192359. Allogeneic neural stem cells which are genetically modified to express carboxylase were implanted into the tumour. These cells are expected to make the tumour cells respond more to irinotecan hydrochloride treatment than if the latter is given alone. Patients are then followed short term up to 3 and 6 months and long term annually for 15 years.

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

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NEURODEGENERATIVE DISEASES

Over the past 30 years, neurodegenerative diseases have also been the focus of regenerative cell-based research. Specifically, in Parkinson's disease (PD), Grealish et al. (2014)[14] showed how to direct human embryonic stem cells into dopamine neurons. These neurons were then used as replacement cell-based therapy in a rat model of PD. It was found that there was acceptable restoration of motor function. This provided a preclinical platform for a clinical translation study.

Indeed, a clinical study (ClinicalTrials.gov Identifier: NCT02452723) using neural stem cells was started in July 2016. Its aim is to evaluate their safety in 12 PD patients. Its completion date is June 2020. Garitaonandia et al. (2018)[15] commented that human parthenogenetic-derived neural stem cells, ISC-hpNSC, were used in this study. Parthenogenetic stem cells are derived from human egg cells and act as embryonic cells. Under MRI-guided surgery, these cells were implanted bilaterally in the substantia nigra, putamen and caudate nucleus. It is expected that the preclinical results in the animal models are reflected in this human trial.

Clinical studies using stem cells are also underway in patients with Alzheimer's diseases. One such study is ClinicalTrials.gov Identifier: NCT02600130, which was started in August 2016 and is estimated to be completed in 2020. It is a Phase I, prospective, randomized, placebo-controlled, double-blinded study designed to test the safety and efficacy of Longeveron Mesenchymal Stem Cells for the treatment of subjects with clinically diagnosed Alzheimer's disease.

In another two clinical trials (ClinicalTrial.gov identifier NCT01297218 and NCT01696591) on patients with Alzheimer, Kim et al. (2015)[16] used MSCs derived from human umbilical cord blood and injected them stereotactically into the hippocampus bilaterally and the right precuneus. The studies were safe and well tolerated and served as platform for further trials to test effectiveness.

Another use of stem cells in neurological diseases is to screen drugs. Little et al. (2019)[17] derived neurons from iPSCs and are trying to use them as *in vitro* disease models of neurological diseases. Specifically, they propose to study the underlying disease mechanisms and screen drugs as potential treatments.

Several clinical trials have also been done for amyotrophic lateral sclerosis (ALS) therapy using stem cells. One such study carried out by Sykova et al. (2017)[18] used bone marrow-derived mesenchymal stem/stromal cells (BM-MSCs) in a nonrandomized, open-label clinical trial (phase I/IIa, EudraCT No. 2011-000362-35). The stem cells harvested were expanded and approximately 15 million cells were delivered to the cerebrospinal fluid through a lumbar puncture. The authors concluded that this intrathecal delivery of BM-MSCs in ALS patients was safe and reduced ALS progression.

SPINAL CORD INJURIES

Spinal cord injury is another candidate for stem cell therapy. Geron Corporation, a late-stage clinical biopharmaceutical company, was the first to start a clinical human trial using human embryonic stem cells directing them to become oligodendrocyte progenitors, which were then used to treat spinal cord injuries. However, they stopped this trial to focus on cancer treatments. Nevertheless, Asterius Biotherapeutics, another biotechnology company, took over the trial. Indeed, they carried out a phase 1 safety trial. The trial involved patients who suffered recent cervical spinal cord injuries leaving them paralysed from the neck down. The human embryonic cell-derived oligodendrocyte progenitor cells (OPCs) were implanted directly into the cervical spine seven days after the injury took place. They concluded that the trial proved the safety of the procedure and that they observed motor function improvements in the upper limbs. In 2017, Manley et al. published a paper on the results.[19]

STROKE

Allogeneic MSCs derived from adipose tissue were used in patients who suffered ischaemic stroke.[20] The cells were injected intravenously within a 2-week time frame after the stroke. Similarly, Hess et al. (2014),[21] in a phase II double blind trial gave intravenously MSCs 24-36 hours after the stroke. No clinical benefits were reported.

In 2016, Kalladka et al.[22] reported the results of their phase 1 study called PISCES, registered with ClinicalTrials.gov Identifier: NCT01151124. They used human neural stem cells in patients (males 60 years and over) suffering from chronic ischemic stroke. This study was carried out after promising improvement was observed in a similar study in rats. In the human study, single doses of 2, 5, 10 or 20 million human neural stem cells where implanted intracerebrally into the putamen. Brain images and clinical observation were carried out over two years. They reported that there were no adverse effects and patients showed improvement in their neurological functions. The patients will be followed for eight years.

Research is also ongoing in haemorrhagic strokes. Indeed, Huang et al. (2019)[7] derived MSCs from bone marrow and delivered them intraventricularly in haemorrhagic stroke animal models. They showed improvement in behaviour and brain damage. Besides they showed that this method is safe and that the stem cells were anti-inflammatory and encouraged neurogenesis. This is promising because external ventricular drain is used to ease intracranial pressure and on occasions to administer medications in patients with intracerebral haemorrhage.

INFLAMMATORY BOWEL DISEASES

Stems cells have anti-inflammatory and immune modulatory effects. These functions are being used as a therapeutic potential in a clinical trial (ClinicalTrials.gov Identifier: NCT03299413) which started in June 2017 and ending in January 2020. Here MSCs are being either injected into the inflamed large intestine or given parentally. It is hoped that there will be a reduction or eradication of the bowel inflammation. If this clinical trial gives positive results, stem cell-based therapy may become a part of the standard treatment algorithm, particularly for refractory IBD cases.

enough already.

It's time to prevent migraine with Aimovig®.

First and only therapy of its kind, specifically designed to prevent migraine by targeting the CGRP receptor[1]

Consistent and sustained efficacy across the migraine spectrum[1-3,6]

Placebo-like safety and tolerability profile[7]

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Simple, once every 4 weeks administration with no loading dose[1]

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Release the grip of migraine[1-5]

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

PRESENTATION:
70mg Solution for injection in pre-filled pen. Each pre-filled pen contains 70 mg (erenumab).
140mg Solution for injection in pre-filled pen. Each pre-filled pen contains 140mg (erenumab).

INDICATION:
Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

DOSAGE:
Adults: Treatment is intended for patients with at least 4 migraine days per month when initiating treatment with erenumab. The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks. Each 140 mg dose is given either as one subcutaneous injection of 140 mg or as two subcutaneous injections of 70 mg. Clinical studies have demonstrated that the majority of patients responding to therapy showed clinical benefit within 3 months.
Pediatric patients: The safety and efficacy of Aimovig in children below the age of 18 years have not yet been established. No data are available.
Special populations: ♦ *Elderly* (aged 65 years and over): Aimovig has not been studied in elderly patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age. ♦ *Renal impairment / hepatic impairment*: No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment.
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 (ethinylestradiol/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 erenumab 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

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NOVARTIS

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Gregoire et al. (2017)[23] in a review article states that 50% of 200 patients who had refractory fistulas because of Crohn's disease and were injected locally with MSCs had complete response. Similar promising results were also observed in patients with luminal Crohn's disease who received allogeneic MSCs administered systemically by an infusion.

CARDIAC INFARCTION AND HEART FAILURE

Research clinical entities are proposing stem cell transplantation as an option for severe heart failure when conventional or interventional treatments fail or if heart transplant is not feasible. There is still some debate as to what stem cell type is best to use. But various clinical research entities have used MSCs for patients with severe myocardial infarction. Autologous MSCs derived from bone marrow were not effective.[24] However, MSC transplants derived allogeneically showed some benefits.[25,26] Ascheim et al. (2014)[27] also showed some benefits in patients who had MI and who were treated with intramycocardial injections of MSCs.

Evidence is showing that generally when stem cells that have a phenotype that is similar to the phenotype of the cells of the recipient tissue are used, patients fair much better. In this context Assistance Publique-Hopitaux de Paris, a Parisian university hospital trust, have conducted a phase I clinical trial named ESCORT (Clinicaltrials.gov Identifier: NCT02057900).) They used human embryonic stem cells that were driven towards a cardiac phenotype fate *in vitro* before their transplantation. Since intramyocardial injections come with documented disadvantages, they carried out the stem cell transplant during coronary artery bypass or mitral valve surgical interventions. Specifically, a fibrin gel patch embedding the progenitor cells (8.2 million interquartile range (IQR): 5 to 10 million) was placed onto the epicardium of the infarcted area and then covered with an autologous pericardial flap. In 2018, Menasche et al.[28] published their outcome stating that the trial was safe and it provided a platform for efficacy studies.

As mentioned above, MSCs have been used in the treatment of MI. Several theories have been put forward on the mechanism of action of MSCs. One is that the MSCs transdifferentiate to cardiac muscle cells. An alternative proposal is that the MSCs secrete paracrine factors such as vascular growth factors which in turn promote angiogenesis and myocardial perfusion, suppress inflammation, and inhibit apoptosis (programmed cell death). Another theory is that they augment repair by stimulating the resident cardiac stem cells to do the above. This latter scenario is more favoured.

EYE DISEASE AND INJURY

Progress in stem-cell based therapy for eye disease and injury is notable. This is due to several factors: surgery is more accessible, assessment of progress is easy, and less stem cells are needed Moreover, the untreated eye can act as a control.

Trials on macular degeneration have been done, as it is a major cause of blindness. Cotrim et al. (2017)[29] concluded that intravitreal injections of CD34+ stem cells derived from bone marrow is safe and showed promising functional improvements.

RESEARCH CLINICAL ENTITIES ARE PROPOSING STEM CELL TRANSPLANTATION AS AN OPTION FOR SEVERE HEART FAILURE WHEN CONVENTIONAL OR INTERVENTIONAL TREATMENTS FAIL OR IF HEART TRANSPLANT IS NOT FEASIBLE. THERE IS STILL SOME DEBATE AS TO WHAT STEM CELL TYPE IS BEST TO USE. BUT VARIOUS CLINICAL RESEARCH ENTITIES HAVE USED MSCS FOR PATIENTS WITH SEVERE MYOCARDIAL INFARCTION.

Stem cells are also being successfully used to regenerate damaged corneal epithelia. Regeneration of the corneal epithelium usually involves stem cells located in the limbus. However, some eye injuries can result in limbal stem cell deficiency (LSCD). When LSCD is severe or total, limbal stem cell transplantation is the best treatment. But alternative stem cell sources are also being contemplated.

Stems cells are also being investigated in cataract research and treatment. Even though known risk factors (like smoking, age, diabetes mellitus and drugs) are associated with cataract development, little is known about the pathological molecular mechanisms. Patricia Murphy et al. (2018)[30] have used pluripotent stem cells and generated light-focusing micro-lenses. These micro-lenses potentially provide avenues to study the molecular mechanisms associated with the known risk factors and to screen drugs to treat or slow cataracts.

ARTHRITIS

MSCs have immuno-suppressive and healing properties which are being exploited to treat various bone disorders like rheumatoid arthritis (RA).[2] In March 2011 a clinical study (ClinicalTrials.gov Identifier: NCT03333681) was started to treat refractory RA. The study ended in 2013. The objectives of the study were the evaluation of safety and tolerability of using MSCs and to get preliminary statistics on their effectiveness. Specifically, patients with refractory RA received intravenously, allogeneic MSCs derived from adipose tissue, which were then expanded *in vitro*. In 2017 Alvaro-Gracia et al.[31] published their results and concluded that the intravenous infusion was safe and tolerable and that they observed clinical efficacy which justified further studies.

Shadmanfar et al. (2018)[32] also exploited MSCs, this time derived from bone marrow. These stem cells (40 million) were implanted intra-articularly in the knee joint of patients with RA. They observed clinical improvements but not after 12 months of the implantation. However, the procedure, besides being safe and tolerable, was also associated with decreased use of methotrexate and prednisolone.

Similarly, Emadelin et al. (2018)[33] implanted MSCs intra-articularly derived from bone marrow to treat osteoarthritis in the knee joint. They showed that these stem cells offered noteworthy pain relief for 6 months when compared to the placebo group.

SYSTEMIC SCLEROSIS, MULTIPLE SCLEROSIS, SYSTEMIC LUPUS ERYTHEMATOSUS

Autologous haemopoietic stem cells have been used in patients with life-threatening autoimmune diseases that were resistant to conservative therapy. The stems cells acted as immunosuppressants and brought about noticeable and encouraging remissions in a high percentage of patients. The commonest auto-immune conditions treated with Hematopoietic Stem Cell Transplantation are systemic sclerosis and multiple sclerosis.

Other diseases were also treated. For example, Burt et al. (2006)[34] conducted a non-randomized clinical trial (ClinicalTrials.gov Identifier: NCT00271934) using autologous HSCs and observed improvements in the enrolled patients with systemic lupus erythematosus who had visceral dysfunctions. Further to this, Huang et al. (2019)[35] showed the effectiveness of using autologous HSCs in patients with lupus nephritis that was refractory to conservative treatments.

DIABETES MELLITUS

Autologous stem cells (ASCs) are being used as stem cell therapy in DM, because their use eliminates the risk of rejection. However, the use of embryonic stem cells raises ethical issues and is associated with high rates of rejection. Thus, in 2007, Zhao et al.[36] isolated ASCs that could make insulin from peripheral blood. A clinical trial on type 1 diabetics found that most of the participants did not need insulin injections after transplanting HSCs.[37]

Currently, ViaCyte, a US biotech company, is conducting research on type 1 diabetes mellitus.[38] ViaCyte is trying to develop two products using stem cells to replace pancreatic beta islet cells. These stem-cell based products are devices that are envisaged to be implanted subcutaneously. The implants contain embryonic stem cells that differentiate into pancreatic progenitor cells which later change to mature insulin-secreting beta-cells that respond to glucose levels physiologically.

HEARING LOSS

The clinical trial with ClinicalTrials.gov Identifier: NCT02038972 was started in January 2013 and completed in January 2017. It involved 11 children (6 weeks to 6 years old) with acquired sensineuronal hearing loss. Its aim was to try to repair or to reverse the acquired sensorineural hearing loss using autologous human umbilical cord blood administered as a single infusion. In mouse and guinea pig models, administration of human umbilical cord blood (hUCB) confirmed the regrowth of the hair cells in the organ of Corti. In 2018, Baumgartner et al.[39] published a paper with the results. Specifically, they conclude that hUCB given intravenously was safe in the participating children and there was a statistically significant reduction in Auditory Brainstem Response (ABR)[28] threshold. Simply, an ABR is a test to determine the ability of the child to hear. Certain neurological 'markers' are registered when a child's hearing nerves respond to the sounds. Thus these markers roughly indicate the child's hearing level. Thus, a reduced ABR result in the trial is a positive and promising finding.

OTHER

Stems cells are also being utilized in basic developmental biology, helping researchers to understand cell types and tissues during the development of the embryo. Specifically, developmental biology studies how genes steer cell growth through differentiation of cells from the stem cell stage onwards. Thus, ultimately it can help to find new ways to be used in regenerative medicine.

Another role of stem cells is in drug development. In short, stem cells are being utilized to enable quick screening of drugs or chemicals, thus reducing testing on animals. Besides such testing using human stem cells addresses the fact that approximately 70% of drugs tested on animals fail during clinical trials, either because they have no effect or due to toxicity (mostly on the heart and liver). Moreover, stem cells can generate cell types that are hard to attain, like neurones, on which testing can be carried out. Another innovative stem cell application in this area is to harvest stem cells from individuals to help in designing personalized medicines. It is well known that there is great variation in drug liver metabolism probably due to differences in liver enzymes such as cytochrome P450 enzymes. iPSCs have the potential to remedy this. Indeed, with iPSC technology, patient-derived iPSCs can be utilized to generate liver cells (and other cell types) and these can then be used for toxicity testing. Thus it is clearly evident that stems cells have an important potential in the development of safer, cheaper, and better drugs.

Stem cells are also being researched in gene therapy. For example, theoretically, HSCs isolated from the blood, can be cultured and any defect corrected by gene editing. Subsequently, the patient receives chemotherapy which eradicates all resident HSCs; this is then followed by a transfusion of edited cells.

CONCLUSION

Stem cell research is catalysing a revolution in medicine. It has the potential to transform algorithms of conventional treatment, especially in many distressing and refractory diseases. The public is already increasingly turning to medical professionals asking for this novel treatment especially as anti-aging and cosmetic treatments. But misconceptions about stem cells as being miracle cells that can cure all ailments are flourishing. As discussed, encouraging results have been observed from

several clinical trials. But it is still early and further research through regulated clinical trials are needed to ascertain their efficacy and safety in medical applications. Moreover, before stem cell therapy is used clinically, one needs to fully understand the behaviour of stem cells upon transplantation and the mechanisms involved when they interact with the diseased or injured micro-environment.

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Dosage	
children aged 2 to 5 years [1-3]	2.5ml every 4-6hrs as required
children aged 6 to 11 years [1-3]	5ml every 4-6hrs as required
adults (including the elderly) and children aged 12 years and over [4-6]	10ml every 4-6hrs as required

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: DMCough** Linctus, Expectorant, Syrup: Amber glass bottle x 100ml.**Marketing** Authorisation Holder: GlaxoSmithKline(Ireland) Ltd. **Marketing** Authorisation Number: **MA** 192/02001-6. Legal category: **POM – Actifed DM** Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years. **OTC – Actifed DM** Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years. Date of preparation: October 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)

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DR PIERRE VASSALLO

IMAGING CANCER OF THE RECTUM

THE IMPORTANCE OF ACCURATE STAGING IN TREATMENT PLANNING

Colorectal cancer is the third most common cancer in men and the second most common in women worldwide.[1] It is the third leading cause of death in both sexes. The prevalence is higher, while mortality rate is lower in developed countries. However, there has been an increasing prevalence in patients under 50 years of age, and in these cases the mortality rate is also increasing.[2,3]

The prognosis of rectal cancer is directly related to tumour involvement of the mesorectum and the ability to achieve complete resection with tumour-free margins.[4] The ability of MRI to depict the the mesorectum and the extent of its involvment by the tumour has significantly improved treatment planning and outcomes. Figure 1 shows the rectum surrounded by the mesorectum, the latter being delimited by the mesorectal fascia (MRF). The most effective treatment for rectal cancer is complete surgical excision of the mesorectum, also known as Total Mesorectal Excision (TME). For tumours involving the MRF, also known as Locally Advanced Rectal Cancers, neoadjuvant chemoradiotherapy can be used to shrink the tumour prior to TME. It is important to note that the mesorectum thins out as it extends inferiorly and is absent at the level of the anal sphincters.

Neoadjuvant chemoradiotherapy results in a significant tumour downstaging in around half the patient treated, while in almost a third of patients complete resolution of the tumour is observed. In the latter cases, some authors recommend follow-up with no surgical intervention.

Thus MRI of the rectum is used to distinguish patients who can go directly to surgery from those who would benefit from neoadjuvant chemoradiotherapy. In addition, it allows assessment of the effectiveness of neoadjuvant chemotherapy, tailored surgical planning and post-operative follow-up/restaging for tumour recurrence.[5] Poor prognostic factors such as extramural vascular invasion and mucin content can also be detected by MRI.

Figure 2 describes the staging rectal cancer based on MR findings, where T refers to tumour size/extent, N relates to the extent of lymph node disease and M refers to the presence and extent of distant metastases.[6] T1, T2 and T3a and b tumours are treated directly with TME. T3c and d combined with N1 lesions receive short term radiotherapy followed by TME. T3 MRF+, T4 or N2-staged lesions receive neoadjuvant chemotherapy and long term radiotherapy followed by a restaging MRI scan.

There are different types of TME, which are based on the distance of the tumour from the anal sphincters. For tumours located in the upper and middle rectum, a *low anterior resection* is performed, which preserves the inferior portion of the rectum and anal sphincters and allows colorectal anastomosis. An *ultra-low anterior resection* may be possible in inferior rectal tumours, in which the colorectal anastomosis is performed 1cm below the tumour margin. For tumours less than 1cm from the anal verge an *abdominal perineal (AP) resection* is employed with excision of the anus and sphincters and formation of a permanent colostomy. An *intersphincteric AP resection* may be possible with sparing of the external sphincter. For more extensive tumours that infiltrate the external sphincter or levator ani muscles, an *extraelevator AP resection* may be performed which includes a broader dissection of the perineal muscles.

MRI staging of rectal cancer is based on Fast Spin Echo T2-weighted images without fat suppression. These provide clear distinction between the bowel wall layers, mesorectal fat and mesorectal fascia. The axial planes assess extent of invasion of bowel wall layers (Fig 3). Sagittal and coronal images depict the level of the tumour (upper, mid or lower rectum: 10.1-15cm, 5.1-10cm and 0-5cm from the anal verge) (Fig 4a). Coronal images are also used to assess involvement of the internal or external anal sphinters (Fig 4b). Infiltration of the anterior peritoneal reflection, which is the peritoneum extending between the rectum and uterus or bladder, raises the tumour stage to T4a (Fig 5a). While infiltration of adjacent organs such as the prostate (Fig 5b) or seminal vesicles increases tumour stage to T4b.

Additional imaging sequences may be used in restaging including Diffusion- Weighted Imaging (DWI) with B-value >800secs/mm^2 (Fig 6a) or contrast-enhanced fat-satuated T1-weighted imaging (Fig 6b). These imaging sequences are not required in the initial staging of rectal cancer, but they are useful for assessing residual tumour after chemoradiotherapy or surgery and for detection of tumour recurrence.

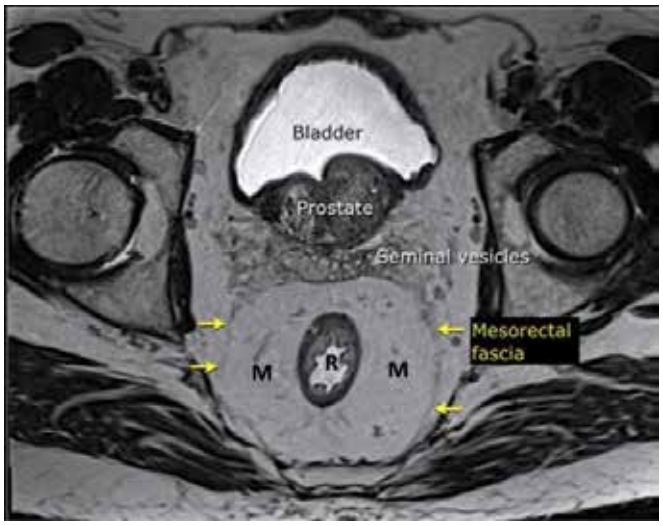

Figure 1. The mesorectum (M) surrounds the rectum (R) and is delimited by the Mesorectal Rectal Fascia (arrows).

Table 1: TNM Staging of Rectal Cancer

***T*-staging is based on direct tumor extension through bowel wall and MRF**

T1 and T2 tumours are limited to the bowel wall:

- T1: involves mucosa+/- submucosa
- T2: involves muscular layer

T3 tumours grow through the bowel wall and infiltrate the mesorectal fat

- T3a: < 1mm extension beyond muscularis propria
- T3b: 1-5 mm extension beyond muscularis propria
- T3c: 5 - 15 mm extension beyond muscularis propria
- T3d: > 15 mm
- T3 MRF+: tumor within 1mm of MRF
- T3 MRF-: no tumor within 1 mm of MRF

T4 tumours extend beyond the MRF

- T4a: involves the peritoneum
- T4b: involves an adjacent organ (e.g. seminal vesicles, bladder)

***N*-staging is based on the number of suspicious lymph nodes**

- N0: no suspicious nodes
- N1: 1-3 suspicious nodes
- N2: ⩾ 4 suspicious nodes

***M*-Staging based on extent of distal metastases**

- M0: No distant metastases
- M1: Distant metastases present
  - M1a: confined to one organ (e.g. liver, lung, distant lymph nodes)
  - M1b: more than one organ or site or peritoneal involvment

Based on AJCC guidelines (6)

Figure 2. TNM staging of rectal cancer. T refers to *T*umour size/extent, N relates to the extent of lymph *N*ode disease, M refers to the presence and extent of distant *M*etastases.

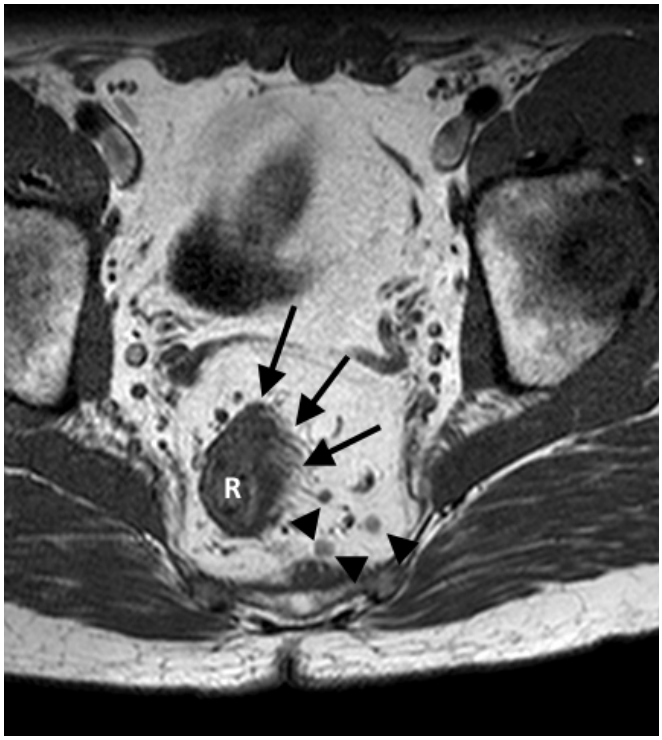

Figure 3. Para-axial T2-weighted MR scan through the rectum (R) showing >5mm infiltration into the mesorectum (arrows) and >3 suspicious mesorectal lymph nodes (arrowheads) (Stage T3cN2). *Case courtesy of Dr Natalie Yang, Radiopaedia.org, rID: 6990.*

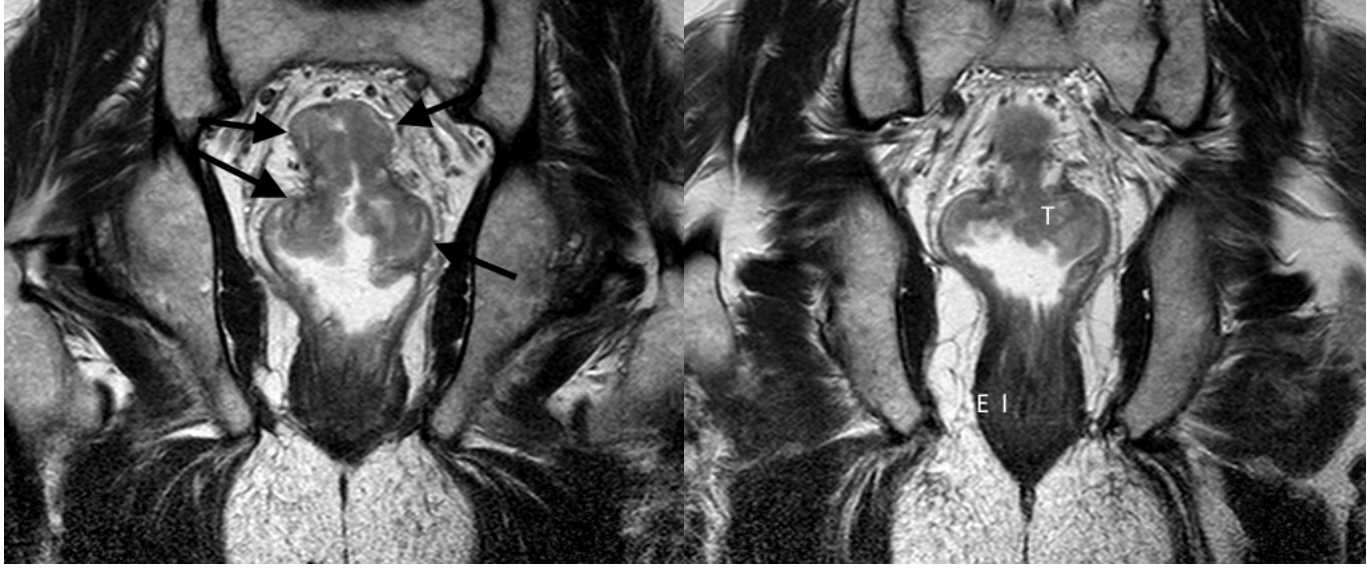

Figure 4. a. Coronal image T2-weighted MR scan through the rectum showing a rectal cancer (arrows). The level of the cancer is best assessed on sagittal and coronal images. *Case courtesy of Dr Natalie Yang, Radiopaedia.org, rID: 7124.* **b.** Sparing of the internal (I) and external (E) anal sphincter is best confirmed on coronal T2-weighted images. (T – tumour) *Case courtesy of Dr Natalie Yang, Radiopaedia.org, rID: 7124.*

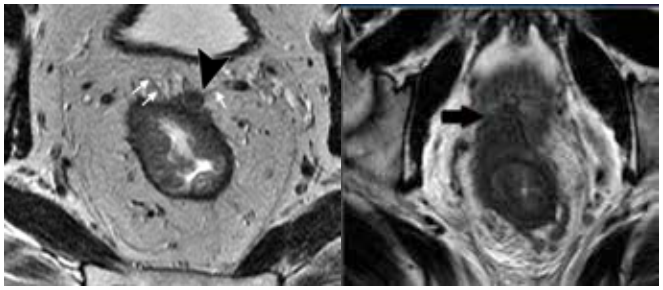

Figure 5. Infiltration of the MRF, peritoneum and adjacent organs can be assessed with axial T2-weighted images. **a.** Infiltration of the peritoneal reflection (arrowhead) between the bladder and rectum (arrows) (stage T4a). **b.** Infiltration of the prostate (arrow) (stage T4b).

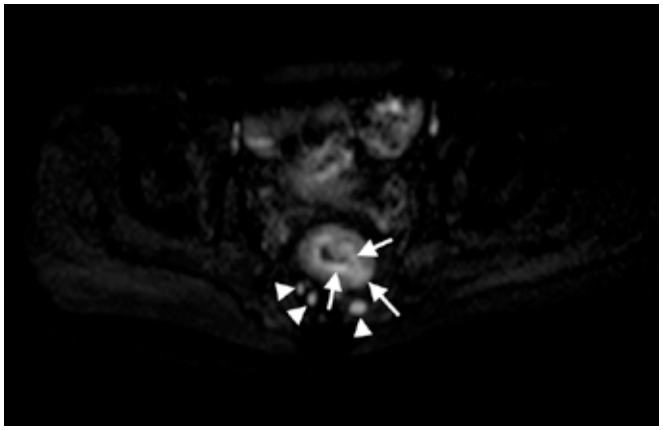

Figure 6a. Transverse DWI image with high B-value taken through the mid-rectum following chemoradiotherapy shows areas of residual tumour as bright areas within the rectum and mesorectum (arrows) as well as in involved lymph nodes in the mesorectum (arrowheads) (Stage T3N1). *Case courtesy of Dr Natalie Yang, Radiopaedia.org, rID: 7135.*

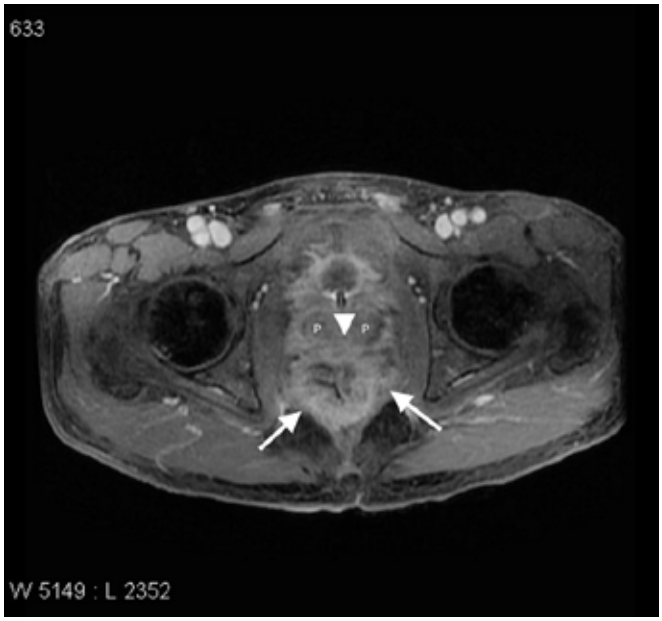

Figure 6b. Contrast-enhanced fat-saturated T1-weighted scan of the rectum following chemoradiotherapy showing tumour invading beyond the mesorectum (arrows) and the prostate (arrowhead) (P – prostate) (Stage T4b) *Case courtesy of Dr Natalie Yang, Radiopaedia.org, rID: 6989.*

The above article provides but a superficial overview of the capabilities of MRI in staging rectal cancer. Numerous important details relating to imaging finding and staging of rectal cancer have been omitted here for the purpose of maintaining simplicity. More extensive and specific literature on the capabilities of MRI for rectal cancer staging is included in the references section. MRI of the rectum is an established and indispensible tool for staging rectal cancer and for monitoring response to therapy.

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