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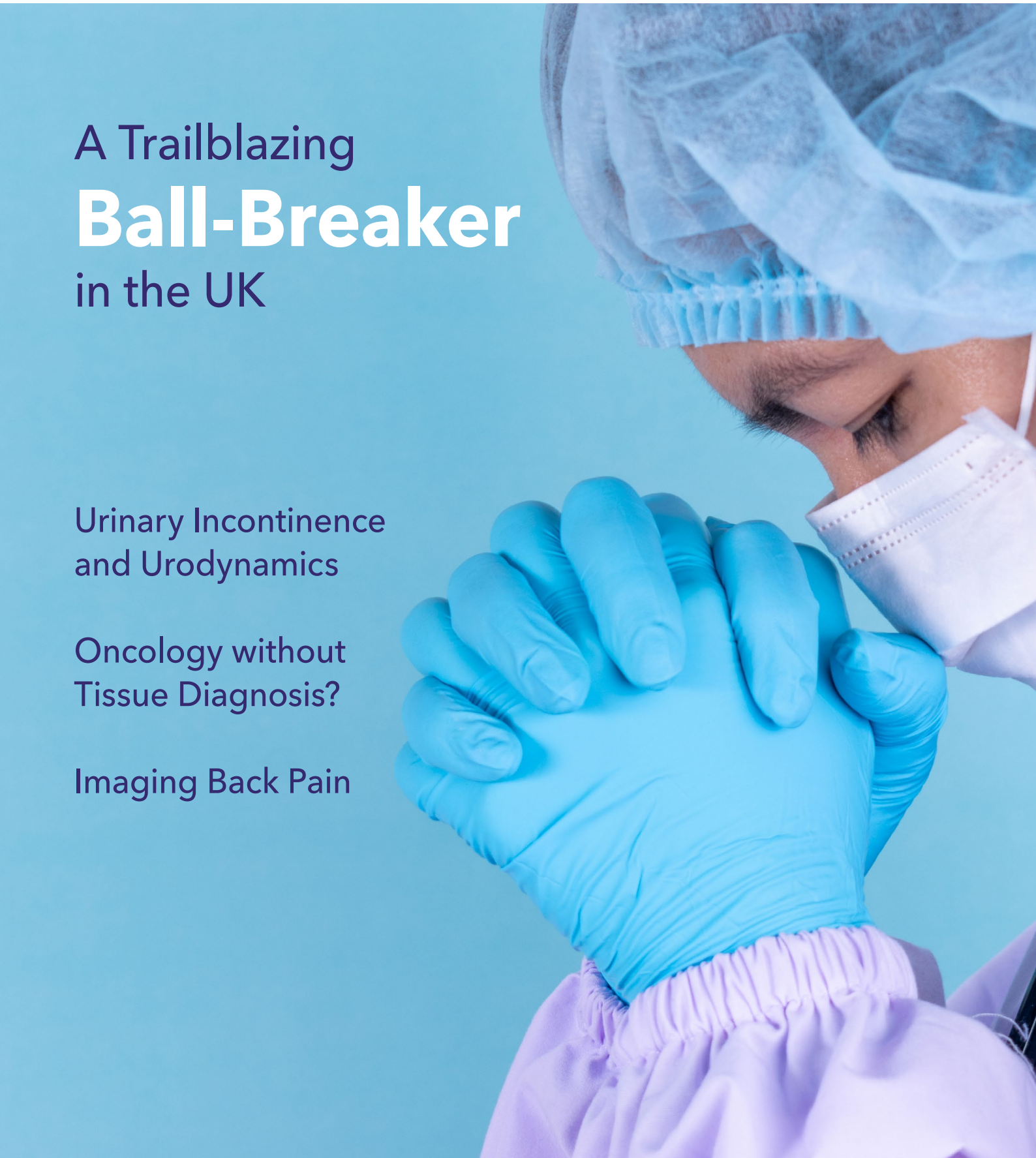
thesynapse

THE MEDICAL PROFESSIONALS' NETWORK



A Trailblazing **Ball-Breaker** in the UK

Urinary Incontinence and Urodynamics

Oncology without Tissue Diagnosis?

Imaging Back Pain

ENTRESTO® (sacubitril/valsartan) **Presentation**: Each film-coated tabletof 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. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co-administered with another ARB containing medicinal 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 sacubitril/valsartan 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 sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartanis 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 sacubitril/valsartan is not recommended. Use of sacubitril/valsartan 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. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Hyperkalaemia: Treatment 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 . If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartanimmediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It 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 (ChildPugh 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 sacubitril/valsartan 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 sacubitril/valsartan with statins or PDE5 inhibitors. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartanis 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 sacubitril/valsartan who are taking NSAIDs concomitantly. Interactions between sacubitril/valsartan 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 sacubitril/valsartan and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan 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 sacubitril/valsartan 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 sacubitril/valsartan with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of sacubitril/valsartan 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 sacubitril/valsartan 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 sacubitril/valsartan 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; Entresto49 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. 2020-MT-ENT-25-JUN-2020

References: 1. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;21(10):1169-1186. 2. Claggett B, Packer M, McMurray JJV, et al; for the PARADIGM-HF Investigators. Estimating the long-term treatment benefits of sacubitril-valsartan. *N Engl J Med.* 2015;373(23):2289-2290. 3. Lewis EF, Claggett BL, McMurray JJV, et al. Health-realted quality of life outcomes in PARADIGM-HF. *Circ Heart Fail.* 2017; 10(8):e003430. 4. ENTRESTO Summary of product characteristics. European Medicines Agency website. http://www.ema.europa.eu. Accessed 2020.

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Entresto® sacubitril/valsartan

Authors

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Issue Guide

TheSynapse

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OUR COLLABORATORS

GMS GERMAN-MALTESE MEDICAL SOCIETY

MMSA Malta Medical Students' Association

MPSA

MADS Malta Association of Dental Students

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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Strong glycaemic control[1], in a simple and patient-friendly administering device[2]

Proven CV protection in a wide range of T2DM patients[3]

REWIND®
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trulicity®
dulaglutide once-weekly injection

TRULICITY® PRESCRIBING INFORMATION
(dulaglutide)
Presentation: Dulaglutide solution for injection in a pre-filled pen. Each single-use pen contains either 0.75 mg or 1.5 mg of dulaglutide in 0.5 ml solution. **Uses** Dulaglutide is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes. **Dosage and Administration:** *Monotherapy*: Recommended dose 0.75 mg once weekly. *Add-on therapy*: Recommended dose 1.5 mg once weekly. For potentially vulnerable patients, 0.75 mg once weekly can be considered as a starting dose. Trulicity is administered as a subcutaneous injection in the abdomen, thigh, or upper arm. It should not be administered intravenously or intramuscularly. The dose can be administered at any time of day, with or without meals. When Trulicity is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued. When Trulicity is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued. When it is added to existing sulphonylurea or insulin therapy, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Trulicity therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended. *Elderly*: No dose adjustment is required based on age. *Renal impairment*: No dose adjustment is required in mild, moderate or severe renal impairment (eGFR < 90 to ≥ 15 mL/min/1.73 m²). Not recommended in end stage renal disease (< 15 mL/min/1.73 m²). *Hepatic impairment*: No dose adjustment is required. *Paediatric*: The safety and efficacy of dulaglutide in children < 18 years have not been established. No data are available. **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Special Precautions:** Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Dulaglutide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin. Dehydration, sometimes leading to acute renal failure or worsening renal impairment, has been reported in patients treated with dulaglutide, especially at the initiation of treatment. Many of the reported adverse renal events occurred in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Patients treated with dulaglutide should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal side-effects and take precautions to avoid fluid depletion. Not recommended in patients with severe gastro-intestinal disease, including severe gastroparesis. In clinical trials, acute pancreatitis has been reported in association with dulaglutide. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, dulaglutide should be discontinued. If pancreatitis is confirmed, dulaglutide should not be restarted. Use of dulaglutide in combination with a sulphonylurea or insulin may increase the risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea or insulin. Trulicity is sodium-free (< 1mmol sodium (23 mg) per 1.5 mg dose). **Interactions:** Dulaglutide delays gastric emptying. For oral medicinal products requiring rapid gastrointestinal absorption, or prolonged release formulations, there is potential for altered drug exposure. Dulaglutide should not otherwise affect the absorption of orally administered medications. Interaction studies with specific medicinal products have been conducted. No dose adjustments of paracetamol, atorvastatin, digoxin, lisinopril, metoprolol, warfarin, oral contraceptives, or metformin (immediate release formula) are required when given together with dulaglutide. For further details of these interaction studies, please see the Summary of Product Characteristics. **Fertility, pregnancy and lactation:** Not recommended during pregnancy. Should not be used if breast-feeding. Effect on fertility is unknown. **Effects on ability to drive and use machines:** When used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable Effects:** *Very common (≥ 1/10)*: Hypoglycaemia (when used in combination with insulin, glimepiride, metformin, or metformin plus glimepiride), nausea, diarrhoea, vomiting, abdominal pain. *Common (≥ 1/100 to < 1/10)*: Hypoglycaemia (when used as monotherapy, in combination with metformin plus pioglitazone, or in combination with an SGLT2 inhibitor with or without metformin), decreased appetite, dyspepsia, constipation, flatulence, abdominal distention, gastro-oesophageal reflux disease, eructation, fatigue, sinus tachycardia, first-degree atrioventricular block (AVB). *Uncommon (≥ 1/1,000 to < 1/100)*: Hypersensitivity, dehydration, injection site reactions, cholelithiasis, cholecystitis. *Rare (≥ 1/10,000 to < 1/1,000)*: Acute pancreatitis, anaphylactic reaction, angioedema. *Not Known (cannot be estimated from available data)*: Non-mechanical intestinal obstruction. None of the patients with systemic hypersensitivity developed dulaglutide anti-drug antibodies. **Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Suspected adverse reactrions should be reported to Charles de Giorgio Pharmacovigilance (mobile number: 9974 1387) or cases may be also reported through medicinesauthority.gov.mt/adrportal (Malta Medicines Authority - Medicines Authority,Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000Malta, E-mail: info.medicinesauthority@gov.mt, Telephone: 356 2343 9000 (from 7:30 to 15:45) Helpline: 356 2343 9111 (from 9:00 to 12:00), Fax: 356 2343 9161). Legal Category:** POM. **Marketing Authorisation Numbers and Holder:** EU/1/14/956/002, EU/1/14/956/007. Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands. Cost (Malta only): 139.90 EUR per pack of 2 single use pre-filled pens. **Date of Preparation or Last Review:** October 2019. **Important notice:** Information prepared is for healthcare providers only.Trulicity is dispensing upon prescription only.Before prescribing Trulicity, you are kindly asked to read full Summary of Product Characteristics. More detailed information about Trulicity and last revision of text Summary of Product Characteristics are available from Eli Lilly (affiliate name and contact details below) and on the European Medicines Agency (EMA) website: http://www.ema.europa.eu, and/or on European Commission website: http://ec.europa.eu/health/documents/community-register/html/alfregister.htm.

References:
1. Trulicity prescribing information. **2.** Trulicity instructions for use. **3.** Gerstein et al. Lancet 2019; 394: 121–130.

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Lilly

DR JEFFREY PULLICINO ORLANDO
Executive Chairman of MCST

Walking the Walk ...

Research and innovation are crucial to securing a better future, one which is built on knowledge valorisation. Science has, through the centuries, helped us develop the solutions to the challenges of the present and the future. One must not only acknowledge the commitment of governments in defining research and innovation as a priority and investing in such a fundamental sector, but also the relentless work of researchers - who are inspired by inquisitiveness and exploration.

This year has been a particularly challenging one for us all. World economies have been tested and thwarted with respect to resilience and growth respectively. At the same time, it is widely known that economies that invest in research and innovation tend to be more effective in sustainable growth and development of societal benefits. In fact, it is evident that such investment in research and innovation is largely unaffected by external factors. The COVID-19 pandemic has demonstrated the importance in research and innovation investment resilience. It has taught us that scientific foundations and evidence are key to drive policy making, and that it will be scientific discoveries that lead us out of this pandemic. It is already evident that the scientific advances that are evolving on disease containment and potential treatments in relation to the current pandemic, have already lifted spirits across the business communities - albeit the road to general recovery being a long and arduous one.

Locally, we have seen continued investment in research and innovation, with corresponding research budget increases for local research ecosystem enablers, such as the Malta Council for Science and Technology. The Government of Malta has pledged €5.3M for a COVID-19 R&D Fund, administered jointly by the Malta Council for Science and Technology and Malta Enterprise, boosted the national R&I research funding programme FUSION and new support measures for early stage research, as well as providing for increased internationalisation incentives in the field. However, the recent news of a fully-fledged Ministry dedicated to the sector is a momentous development. A development that will see the establishment of a dedicated public sector structure to further support research and innovation. This will not only further concretise research and innovation as a priority in Malta, but will enable us to think beyond our traditional economic strongholds and move towards developing and incentivising other knowledge-intensive sectors within which we can leverage new opportunities and develop capacity and critical mass. The Malta Council for Science and Technology's ongoing work on *Malta's Smart Specialisation Strategy 2021-2027*, that has been based on extensive public consultation, has harnessed such a focus.

The future does look challenging, an unprecedented pandemic has changed various aspects of national economies and our everyday lives. However, there is a common thread that loops through the past, our present, and into the future - resilience within the research and innovation sector. It is through this sector, that we can continue breaking new ground, whilst developing the solutions to societal and technological challenges.

This mindset and ambition will undoubtedly help create a better and more sustainable future for us all.

Dr Ian Ellul interviews **Professor Dame Clare Gerada**, a few days after being awarded a damehood in the 2020 Queen Elizabeth II's Birthday Honours, for services to General Practice. Based in the UK, Dame Gerada is the first Maltese to attain this prestigious acknowledgement.

A Trailblazing Ball-breaker in the UK

YOUR FATHER DR ANTHONY GERADA WAS A FAMILY DOCTOR HAILING FROM ŻEJTUN AND YOUR MOTHER WAS FROM SLIEMA. IN 1948 THEY DECIDED TO VENTURE IN NIGERIA WHERE THEY STAYED FOR 15 YEARS. WHY EMIGRATE, CHOOSING NIGERIA?

During the forties Nigeria was undergoing a period of rapid modernisation. I clearly remember my father stating, "In Nigeria, the Italians build the roads and Malta provided the doctors". In fact, at that time it was home to approximately ten Maltese doctors. So when my father finished his house jobs in Malta he applied for colonial service and was eventually detailed as medical officer to a large Nigerian community. Now, can you imagine my 20-year-old mother accompanying my father and transitioning from tiny Malta to Nigeria during a period where there was no telephone or no long-haul flights? Really amazing …

IN 1963, WHEN YOU WERE FOUR YEARS OLD, YOUR PARENTS RELOCATED TO PETERBOROUGH. YOUR FATHER SUCCESSFULLY MANAGED TO OPEN SINGLE-HANDEDLY A GENERAL PRACTICE, MAKING INROADS AMONGST THE NUMEROUS ITALIAN IMMIGRANTS. WHY MOVE OUT OF NIGERIA AND GO TO PETERBOROUGH?

In the sixties Nigeria started becoming dangerous because of civil unrest. This was more so for the expat community. So, in 1963, before the civil war broke out, my father decided to move to the UK. Nonetheless, those were challenging times for our family since we were not well-accepted as immigrants. We tried to get accommodation in Liverpool but did not manage, possibly because of our large family of six – I had three siblings – and the fact that we had a foreign-sounding name. However, Peterborough worked well since it was home to the largest Italian community in the UK. My father was fluent in Italian and the Italians did not speak English. Eventually he convinced Dr Joe Pace, today still living in Sliema, as his partner. Later on, the *Gerada and Pace General Practice* enrolled Dr Ray Zerafa, also a Maltese doctor.

DID YOU SPECIALISE IN PSYCHIATRY BECAUSE OF THESE LIFE EVENTS? I REMEMBER INTERVIEWING PROF. MAURICE CAUCHI, A RETIRED PROFESSOR OF PATHOLOGY BASED IN AUSTRALIA, WHERE HE DISCUSSED THE PSYCHOSOCIAL ADVERSITY OF IMMIGRANTS.

I always considered myself as an immigrant. I clearly remember my father saying that, as an immigrant, one must work much harder to achieve the same things and also, that one should give something back to the country which adopted you.

After I graduated from medical school, the natural thing for me to do was to join my father's general practice and become *Gerada & Gerada* since I would not have needed to do additional training. However, I decided to go to London to train in various areas, even though I knew that I wanted to become a GP. I believe

I believe that my father would have been disappointed if I simply joined his practice since he always wanted me to achieve something under my own steam

that my father would have been disappointed if I simply joined his practice since he always wanted me to achieve something under my own steam. Between my surgical shifts I used to visit the library and read about Freud in the *Journal of Psychiatry*. This interest branched into the area of schizophrenia (as there were lots of articles about this illness in the journal). So I decided to study psychiatry and got into the Maudsley hospital because, to be blunt, I wanted to learn more about Freud and schizophrenia. There I met Dr David Cassar, who became a friend of mine, and also my husband-to-be Simon Charles Wessely. I eventually attained my postgraduate exam in psychiatry but afterwards I turned to general practice. This stemmed from the fact that during my training in London I came to realise that I loved every area in medicine. This reaffirmed my conviction that I was a generalist and that my heart was set on general practice.

LIVING YOUR CHILDHOOD DURING POSTWAR BRITAIN MUST HAVE BEEN CHALLENGING. DO YOU BELIEVE THAT YOUR SOCIALIST VIEWS HAVE BEEN SEEDED DURING THAT PERIOD?

Definitely. I used to accompany my father on his medical visits to postwar slums in Peterborough where I saw poverty first-hand … barefoot and hungry children, fifteen children living in two rooms, homes without any inside lavatory, the list goes on. If I close my eyes I can still see them today. Further to this, my school was in a community that at the time included many very poor families which meant that many children who attended there were deprived. In keeping with all this, I knew that I was privileged; my father constantly conveyed the message that I needed to give something back to the community where I belong. This, I remember him saying, starts from being a good observer and listener.

YOU ARE MEDICAL DIRECTOR OF PRACTITIONER HEALTH WHICH IS A NHS SERVICE FOR DOCTORS AND DENTISTS WITH MENTAL ILLNESS AND ADDICTION PROBLEMS. THIS PRACTICE TRACES ITS ORIGINS TO A 2007 WHITE PAPER DRAWN AFTER DR DAKSHA EMSON, A 34-YEAR OLD UK-BASED PSYCHIATRIST WHO SUFFERED FROM BIPOLAR AFFECTIVE DISORDER, COMMITTED SUICIDE AFTER STABBING AND SETTING HERSELF AND HER THREE-MONTH BABY ON FIRE IN 2000. WHAT MAKES YOU SO PASSIONATE ABOUT YOUR WORK?

As you correctly said, both mother and daughter died because the mother felt too ashamed to get help through normal routes. She did have access to support but her psychiatrist retired and she could not open up to the new psychiatrist since he was a college friend of hers. Other healthcare professionals told her, "You are a psychiatrist, you know what you should do". This is, of course, untrue since she was having post-natal psychosis … and she killed herself.

Abortion has three victims…

the mother, father and fetus. However, a woman has a right to her body and her life and should safely access termination of pregnancy

Every time I hear about doctors killing themselves, I ask myself what would have happened if only that doctor came to my service! I won the contract for services in 2008. Anybody who works for me should have what we call 'it' … putting your metaphoric arms around doctors who took considerable courage to come out and seek help … to make them better in a patient-centric setting.

In hindsight I can confidently say that general practice was my calling but later on in life the calling was to look after my own kind.

YOU WERE CHAIR OF THE RCGP BETWEEN 2011 AND 2013. WHAT WAS YOUR LEGACY?

I must start by stating that I have always regretted the fact that my father, who was severely demented, never comprehended the fact that I had risen through the ranks and been elected head of the profession. He would have been so proud!

At the helm of RCGP I faced an unpopular piece of legislation, the 2012 Health and Social Care Bill. No-one seemed to want to rock the boat but I decided to speak out and highlight its flaws - many years later I was proven right. I believe that my legacy was also to take the college to the modern era by stepping up the engagement with its members. This has been reflected by a surge in memberships during my stewardship. This was complemented with public engagement; I was all over the media answering questions and conveying the role of the RCGP to the general public.

I also contributed to shatter the glass ceiling, through merit, when I became the college's *first female* chairperson for 55 years. I believe that this has helped motivate my two fellow female colleagues to become chairs after my term was up. This, together with my other work around the edges, has positioned me as a well-recognised GP amongst peers.

YOU FEEL STRONGLY ON ASSISTED DYING AND ABORTION. HOW DID YOUR PERSONAL EXPERIENCES AND YOUR DECADES OF DISTINGUISHED PRACTICE MOULD YOUR VIEWS?

On assisted dying I am in favour that colleges and medical professions have a neutral view and not use their power to influence people. A recent survey by the British Medical Association has revealed that most doctors either want a change in the law to support assisted dying or want that the Association adopts a neutral position on the matter. I believe that doctors have no more nor less authority than anyone less in coming to a view about assisted dying. Similar to abortion, we would only have more authority if a law is enacted, in that then we would see who is eligible, how it is done, and so on.

Taking abortion, I am in favour of persons having a choice over their bodies. It is quite extraordinary that people in Malta do not have access to legal abortion. Abortion has three victims … the mother, father and fetus. However, a woman has a right to her body and her life and should safely access termination of pregnancy. Having said that, ideally one should not get pregnant in the first place and this stems from access to good contraception. I believe that the Maltese Medical Association might be expected to have a position on this matter, even a neutral one, since it is very powerful.

DO YOU BELIEVE THAT, LAW PERMITTING, A PERSON SHOULD PLAN ONE'S INFIRMITY?

I believe that we, me and you, will be the last generation that does not have a choice relating to care during end-of-life. My hypothesis is that the next generation will have access to legal assisted dying. Although my views on a living will are personal and private, I do believe that the medical profession as a group needs to be neutral on this.

YOU ARE MARRIED TO PROFESSOR SIR SIMON CHARLES WESSELY WHO WAS AWARDED A KNIGHTHOOD FOR SERVICES TO MILITARY HEALTHCARE AND PSYCHOLOGICAL MEDICINE. HE WAS ALSO HANDPICKED BY FORMER UK PRIME MINISTER THERESA MAY TO CONDUCT A REVIEW OF THE MENTAL HEALTH ACT 2007. HOW DO YOU MANAGE YOUR BUSY WORK-LIFE BALANCE, WHICH INCLUDES YOUR TWO SONS?

Early on in our relationship we invested our income to support our ability to work, engaging the services of a cleaner as well as childminding personnel. We also decided to live near work to reduce commute time. Another important decision was that we made regular holidays abroad, going away from it all, as a family. However, we were lucky since we were healthy and we had healthy children.

SINCE 2020 YOU HAVE BEEN CHAIR OF THE CHARITY *DOCTORS IN DISTRESS*. IT WAS SET UP AFTER THE SUICIDE OF DR JAGDIP SIDHU, A UK-BASED CARDIOLOGIST WHO COMMITTED SUICIDE IN 2018. EXPLAIN MORE.

I run a bereavement group for relatives of doctors who committed suicide and the brother of Dr Sidhu was in this group. He set up the charity with the money donated at his brother's funeral. Running a charity is hard work and in 2020 it was either going to fold, otherwise it had to be resurrected. I was invited to take over in March and I accepted. The Charity lifts the lid on suicide and mental stigma and provides support groups for doctors so that they can talk about the emotional impact of their work and not suffer in silence.

RECENTLY WE SAW THE LAUNCH OF YOUR BOOK, *BENEATH THE WHITE COAT – DOCTORS, THEIR MINDS AND MENTAL HEALTH*. WHY SHOULD I BUY IT?

If I do say so myself, it is a really good read, most chapters drawing from my experience at the coalface of the provision of mental healthcare services to the medical profession. The book is a mix of evidence-based academic work together with my personal autobiography, with most chapters written in first person, also mentioning my father and Malta. Readers have told me that the book is easy to read.

The book has some unique chapters on example, autism in doctors which is a subject which, as far as I know, has never been published before. It also has a chapter on bipolar disorders amongst medics, written from my experience of treating 200 doctors with this condition. Other chapters deal with shame, stigma and also, why doctors have high levels of mental problems and suicide rates when they have exceptionally good prognostic features such as job security, high income and intelligence. Possibly in our curricula we are taught that we need to deny our own vulnerability and actually work harder if one feels tired since this could be perceived as a sign of weakness by peers.

IN 2006 THE SYNAPSE, IN COLLABORATION WITH THE MEDICAL ASSOCIATION OF SURGEONS, LAUNCHED MEDICAL ELEARNING MODULES, WHICH WAS A FIRST FOR MALTA. WHAT ARE YOUR VIEWS ON ELEARNING AND DO YOU BELIEVE THAT THEY DECREASE BURN-OUTS AMONGST DOCTORS?

Between 1996 and 2005 I headed the addiction treatment services for primary care in the UK and I was one of the first to develop eLearning modules on addiction. The creation of eLearning looks effortless, but its development is a labour-intensive process, taking several weeks to make it accurate and interactive. It is a very important tool and most of our learning nowadays

is being done digitally. Although eLearning is important it should never completely replace the face-to-face interaction with peers, but rather it should complement it. Covid apart, one must never underestimate the power of meeting humans in person. After all, medicine is all about connectiveness.

COVID-19: HOW DO YOU PERCEIVE THE BALANCING ACT BETWEEN PUBLIC HEALTH AND THE ECONOMY AND WHAT ADVICE WOULD YOU GIVE TO OUR PRIME MINISTER?

Advisers advice and politicians make laws. This renders the work of politicians challenging. As doctors we tend to prioritize health over economic health. Politicians, however, need to find a balance. It is clear now that those who suffer the brunt of this pandemic, including any restrictions which are imposed, are the socially and economically deprived. In the long run the economic problems will cause more harm to this population.

In every generation it is the young who need to make sacrifices. It is the young who go to war … who work as frontliners … It is thus important for my generation to ask what needs to be done to help. I would rather wrap myself in plastic if this means that children go to school. I would rather isolate myself for six months if this means that the young can go to work and earn a living.

We need to support politicians even if, in hindsight, it may appear that they took wrong decisions. A good politician gives us hope with a sense of reality. Also, everyone needs to take cognizance of the sacrifices that need to be done. Let this period be the yellow-brick road to a new way of life based on respect and self-awareness.

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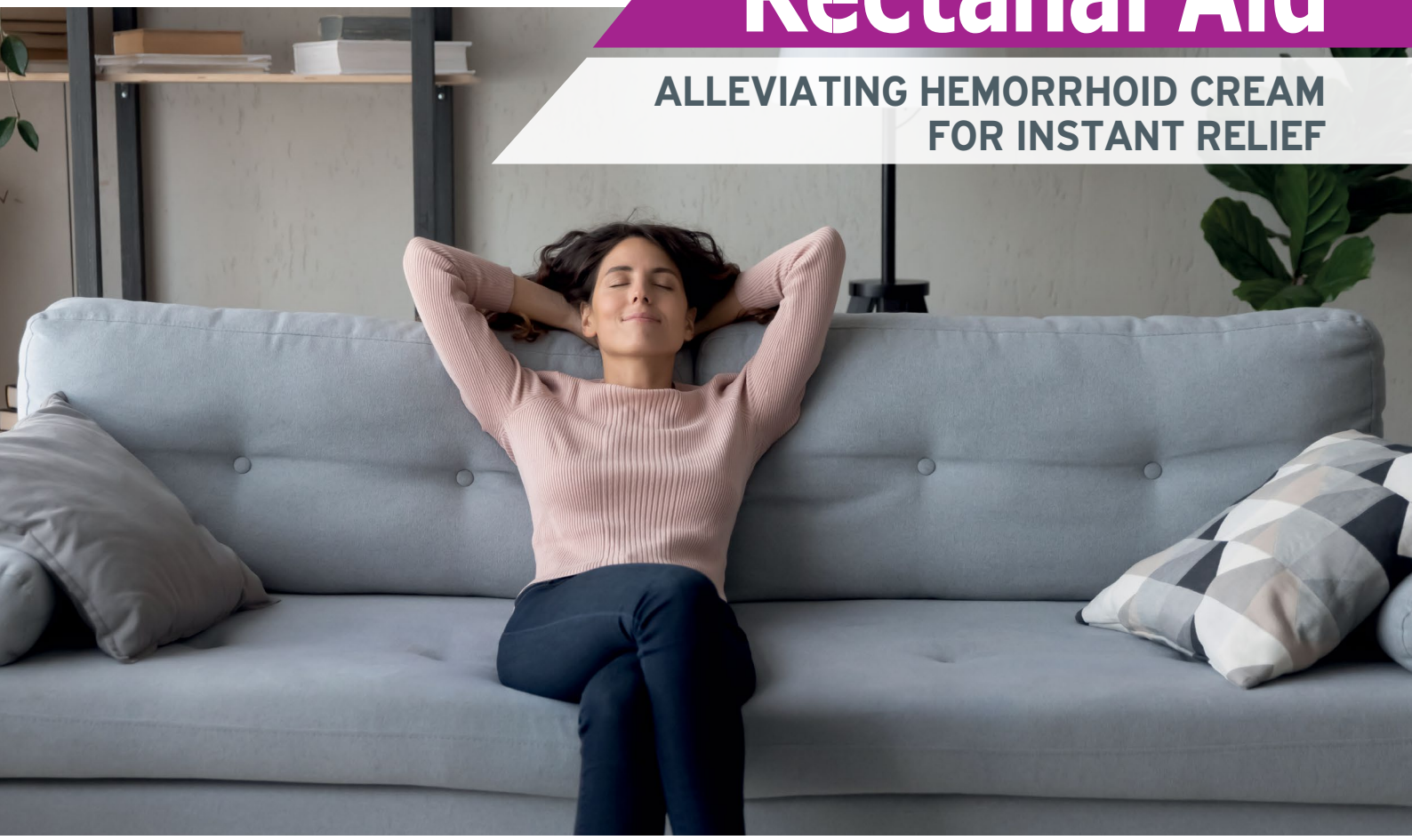

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PROF. ALBERT CILIA-VINCENTI

Oncology
without Tissue Diagnosis?

Most UK NHS hospitals have close educational and working relationships with their referring family doctors, and many of them hold a weekly "grand round" meeting, often accompanied by lunch in the hospital dining room. The various hospital departments, and occasionally GPs, take it in turn to present cases.

The new Charing Cross Hospital in Fulham, London, is no exception. This is 1976 and the Oncology department is presenting a "grand round" case of "radiotherapy without a tissue diagnosis". The presentation describes an English woman in her mid-fifties presenting with pain in the back. Plain X-rays reveal osteolytic lesions in some thoracic vertebral bodies and a small peripheral opacity in one lung. Provisional diagnosis is pulmonary carcinoma with thoracic vertebral metastases.

The presenting team go on to explain that repeated sputum specimens sent for cytology were all negative for neoplastic cells, and the lung lesion is too peripheral to be viewed and sampled bronchoscopically. Biopsy of a vertebral lesion, or the pulmonary lesion, was not carried out. It is possible that in the mid-seventies facilities and/or knowhow to perform needle biopsies from such sites were not yet established.

The presentation concludes that this case is an uncommon example where oncological treatment has to proceed without a tissue diagnosis. The lady is given radiotherapy to the lung and vertebral lesions. A few weeks later she dies and at autopsy the oncology team is dumbfounded to discover that she died from disseminated tuberculosis.

This reminded me of a lecture delivered to us students in 1960s Malta by a Swedish pathology professor, wherein he claimed that 15% of tuberculosis cases in his country were only diagnosed at autopsy. At the time all deaths in Sweden had to undergo an autopsy, so the country had very accurate morbidity and mortality records.

In 1981 I took a month off (used my annual leave) from my UK consultant post to do a histopathology locum in Jeddah, Saudi Arabia. There I met the late Luis Vassallo, physician, who had left Malta because of the doctors' strike and lockout. He came to me one morning to tell me about this Saudi woman patient in her mid-fifties who presented with pain in her back and plain X-rays had shown a lung opacity and osteolytic lesions in thoracic vertebrae.

I couldn't believe the similarity of his case with the Charing Cross Hospital one. However, Luis was convinced this was lung cancer with vertebral metastases and asked me to do a bone marrow on her. I said I was a histopathologist not a haematologist, but he insisted I do it because the haematologist was away on holiday.

I thought confirming disseminated lung cancer from a random bone marrow sampling was rather far-fetched, and I hadn't done a sternal tap since I was a houseman in Malta. Anyway, I managed to get a sternal bone marrow sample which, as to be expected, was normal. However, in the report I added that I had seen a similar case in London which turned out to be disseminated tuberculosis.

Because there were no facilities in Jeddah to biopsy a vertebral or a peripheral pulmonary lesion, the patient was transferred to Riyadh. Just before I left Saudi to return to England, a doctor phoned me from Riyadh to tell me that he had seen my note in this patient's bone marrow report and that I would be pleased to know that a vertebral biopsy had in fact confirmed tuberculosis.

Before anti-tuberculous drugs appeared on the therapeutic scene, thoracic vertebral and para-vertebral tuberculous disease involvement (Pott's disease) was not uncommon and vertebral collapse was responsible for hunchbacks. This unfortunate disfiguring complication was so commonplace it also found its way into literature and theatre, such as the Hunchback of Notre Dame and Rigoletto the hunchback.

Targeting joint symptoms and more in PsA[1]

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(ixekizumab)

Presentation Ixekizumab solution for injection in a pre-filled syringe or pre-filled pen. Each single use pre-filled syringe and pre-filled pen contains 80 mg of ixekizumab in 1 mL solution. The solution is clear and colourless to slightly yellow.
Uses Treatment of moderate to severe plaque psoriasis in • adults who are candidates for systemic therapy. • in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy.Treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies (alone or in combination with methotrexate). Treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy. Treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).**Dosage and Administration Posology Plaque psoriasis in adults** Recommended dose: 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. Paediatric plaque psoriasis (age 6 years and above) The recommended dose given by subcutaneous injection in children is based on the following weight categories: Greater than 50 kg: 160 mg (two 80 mg injections) at Week 0, followed by 80mg every 4 weeks thereafter. 25-50kg: 80 mg at Week 0, followed by 40mg every 4 weeks thereafter. Ixekizumab doses of 40 mg must be prepared and administered by a qualified healthcare professional using the commercial Taltz 80 mg/1 ml prefilled syringe. For instructions on preparation of Taltz 40 mg, see SmPC. Doses less than 80 mg must be prepared by a healthcare professional. For children prescribed 80 mg, Taltz can be used directly from the prefilled syringe. Use the Taltz 80 mg pre-filled pen only in those children that require a dose of 80 mg and do not require dose preparation. Taltz is not recommended for use in children with a body weight below 25 kg. Paediatric body weights must be recorded and regularly re-checked prior to dosing. **Psoriatic arthritis** Recommended dose: 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis. Axial spondyloarthritis (radiographic and non-radiographic) Recommended dose: 160 mg (two 80 mg injections) by subcutaneous injection at Week 0, followed by 80 mg every 4 weeks (see SmPC for further information). For all indications consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks. **Elderly**: No dose adjustment required. Renal or hepatic impairment: Taltz has not been studied in these patient populations. No dose recommendations can be made. Paediatric plaque psoriasis (below a body weight of 25 kg and below the age of 6 years) There is no relevant use of Taltz in children below a body weight of 25 kg and below the age of 6 years in the treatment of moderate to severe plaque psoriasis. **Paediatric psoriatic arthritis** The safety and efficacy of Taltz in children and adolescents aged 2 to less than 18 years in the treatment of psoriatic arthritis (a category of juvenile idiopathic arthritis) have not yet been established. No data are available. There is no relevant use of Taltz in children below 2 years for the indication of psoriatic arthritis Method of administration For subcutaneous injection. Injection sites may be alternated. If possible, areas of skin that show psoriasis should be avoided as injection sites. Must not be shaken. **Contra-indications** Serious hypersensitivity to the active substance or excipients. Clinically important active infections (e.g. active tuberculosis). **Warnings and Special Precautions Infections:** Treatment associated with an increased rate of infections such as upper respiratory tract infection, oral candidiasis, conjunctivitis, and tinea infections. Should be used with caution in patients with clinically important chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If an infection develops, monitor carefully and discontinue if the patient is not responding to standard therapy or if the infection becomes serious. Taltz should not be resumed until the infection resolves. Must not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of Taltz in patients with latent TB. Hypersensitivity: Serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. If a serious hypersensitivity reaction occurs, administration should be discontinued immediately and appropriate therapy initiated. Inflammatory Bowel Disease (including Crohn's disease and ulcerative colitis): Cases of new or exacerbations of inflammatory bowel disease have been reported (see SmPC). Ixekizumab is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, ixekizumab should be discontinued and appropriate medical management should be initiated. **Immunisations**: Should not be used with live vaccines. No data are available on the response to live vaccines: there are insufficient data on response to inactive vaccines. **Excipients**: This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, i.e., essentially "sodium-free". (See SmPC for full information on excipients). **Interactions** Safety of Taltz in combination with other immunomodulatory agents or phototherapy has not been evaluated. In population pharmacokinetic analyses, drug clearance of ixekizumab was not affected by concomitant administration of oral corticosteroids, NSAIDs, sulfasalazine, or methotrexate. When Taltz was co-prescribed with drugs metabolised by CYP3A4, CYP2C9, CYP2C19, CYP1A2 or CYP2D6 in patients with moderate to severe psoriasis no clinically significant impact on the pharmacokinetics of these drugs was found. Fertility, Pregnancy, and Lactation **Women of childbearing potential:** Should use an effective method of contraception during treatment and for at least 10 weeks after treatment. **Pregnancy**: Recommended to avoid the use of Taltz during pregnancy. **Breast-feeding:** A decision should be made whether to discontinue breast-feeding or to discontinue Taltz. **Fertility**: The effect of ixekizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility. Effects on ability to drive and use machines Taltz has no or negligible influence on the ability to drive and use machines.

taltz®
(ixekizumab)

OUR GOAL IS CLEAR. TOUCHABLE. SKIN.

After **1 WEEK** of treatment with Taltz, the average patient has

compared to baseline*

After **2 WEEKS** of treatment with Taltz, the average patient has

compared to baseline*

After **12 WEEKS** of treatment with Taltz, the average patient has

compared to baseline*

extract from Integrated Data Analysis of UNCOVER 2

Taltz, a targeted IL-17A inhibitor with high binding affinity (kd<3 pM) Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy

* measured as percentage decrease in PASI score from baseline

Undesirable Effects **Summary of the safety profile:** The most frequently reported adverse drug reactions were injection site reactions (15.5 %) and upper respiratory tract infections (16.4 %) (most frequently nasopharyngitis). Injection site reactions: The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild to moderate in severity and did not lead to discontinuation of Taltz. **Infections**: In the placebo-controlled period of the phase III clinical studies in plaque psoriasis in adults, infections were reported in 27.2 % of patients treated with Taltz for up to 12 weeks compared with 22.9 % of patients treated with placebo. The majority of infections were non-serious and mild to moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6 %) of patients treated with Taltz and in 3 (0.4 %) of patients treated with placebo. Infection rates observed in psoriatic arthritis and axial spondyloarthritis clinical studies were similar to those observed in the plaque psoriasis studies with the exception of the frequencies of the adverse reactions of influenza and conjunctivitis which were common in patients with psoriatic arthritis. **Paediatric population:** The safety profile observed in children with plaque psoriasis is consistent with the safety profile in adult patients with plaque psoriasis with the exception of the frequencies of conjunctivitis, influenza, and urticaria which were common. Inflammatory bowel disease was also more frequent in paediatric patients, although it was still uncommon. Very common (≥ 1/10): Upper respiratory tract infection, injection site reactions. Common (≥ 1/100 to < 1/10): Tinea infection, herpes simplex (mucocutaneous), oropharyngeal pain, nausea. Laboratory assessment of neutropenia and thrombocytopenia In plaque psoriasis studies, 9% of patients receiving Taltz developed neutropenia. In most cases, theblood neutrophil count was ≥1,000 cells/mm3. Such levels of neutropenia may persist, fluctuate or betransient. 0.1% of patients receiving Taltz developed a neutrophil count <1000 cells/mm3. In general,neutropenia did not require discontinuation of Taltz. 3% of patients exposed to Taltz had a shift froma normal baseline platelet value to <150,000 platelet cells/mm3 to ≥75,000 cells/mm3.Thrombocytopenia may persist, fluctuate or be transient.The frequency of neutropenia and thrombocytopenia in psoriatic arthritis clinical studies is similar tothat observed in the plaque psoriasis studies

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via ADR Reporting, The Medicines Authority , Post-Licensing Directorate, 203 Level 3, Rue D'Argens, GŻR-1368 Gżira; www.medicinesauthority.gov.mt; postlicensing.medicinesauthority@gov.mt

Legal Category POM Marketing Authorisation Numbers and Holder EU/1/15/1085/001, EU/1/15/1085/004. Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

Date of Preparation or Last Review June 2020 **Further Information is Available From** Charles de Giorgio Ltd Triq. Kan. Pirrotta B'Kara, BKR 114, Malta

This medicinal product is subject to additional monitoring. To report any suspected adverse reactions associated to this medicine is important.

Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies. For full prescribing information please refer to your local country product information.

VV code :PP-IX-MT-0014 date of preparation : 22/07/2020

reference:
1.Lilly DoF IXE014 2015 (v1.0)
2.Mease PJ et al Ann Rheum Dis 2020 123

I want an end to my monthly headaches[1]

I want to be free from regular pelvic pain[2,3]

DIFFERENT WOMEN DIFFERENT NEEDS

COULD QLAIRA® BE RIGHT FOR HER TOO?

I want a pill that may improve sexual function[4]

I need a contraceptive pill that will work[5]

Qlaira®

Different needs, one solution

Qlaira® film-coated tablets. Please refer to full Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** Each wallet (28 film-coated tablets) contains in the following order: 2 dark yellow tablets (3 mg estradiol valerate), 5 medium red tablets (2 mg estradiol valerate and 2 mg dienogest), 17 light yellow (2 mg estradiol valerate and 3 mg dienogest), 2 dark red tablets (1 mg estradiol valerate), and 2 white tablets (no active substances). ***Excipients:*** Contains lactose. **Indication:** Oral contraception. Treatment of heavy menstrual bleeding in women without organic pathology who desire oral contraception. **Dosage and Administration**: One tablet is to be taken daily for 28 consecutive days in the order directed on the package at about the same time of day. Missed tablets and gastro-intestinal disturbances may reduce efficacy (see SmPC for guidance). **Contraindications:** Presence or risk of venous thromboembolism (VTE): current, history of, or high risk of deep venous thrombosis (DVT) or pulmonary embolism (PE), known hereditary or acquired predisposition for VTE (e.g. APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency), major surgery with prolonged immobilization. High risk of VTE due to presence of multiple risk factors. Presence or risk of arterial thromboembolism (ATE): current, history of (e.g. myocardial infarction), or high risk of ATE (due to multiple risk factors or to the presence of one of the following serious risk factors – diabetes mellitus with vascular symptoms, severe hypertension or severe dyslipoproteinaemia), or prodromal conditions (e.g. angina pectoris), cerebrovascular disease (current or history of stroke or prodromal condition (e.g. transient ischaemic attack (TIA)), known hereditary or acquired predisposition for ATE (e.g. hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant)), history of migraine with focal neurological symptoms. Presence or history of severe hepatic disease as long as liver function values have not returned to normal, presence or history of liver tumours (benign or malignant), known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts), undiagnosed vaginal bleeding, hypersensitivity to the active substances or to any of the excipients. **Precautions and warnings**: If any of these conditions or risk factors are present, the suitability of Qlaira should be discussed with the woman. In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Qlaira should be discontinued. In case of suspected or confirmed VTE or ATE, combined hormonal contraceptives (CHC) use should be discontinued. Prior to the initiation or reinstitution of Qlaira a complete medical history (including family history) should be taken and pregnancy must be ruled out. Women should be advised that CHC do not protect against HIV infections (AIDS) or other sexually transmitted diseases. In case anti-coagulant therapy is started, adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins). *Risk of VTE:* The use of any CHC increases the risk of VTE compared with no use. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Limited data suggests that Qlaira may have a risk of VTE in the same range. The decision to use any other product (such as Qlaira) than one known to have the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, how her current risk factors influence this risk, and that her VTE risk is highest in the first year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break of 4 weeks or more. Risk factors include obesity (BMI over 30 kg/m^2), prolonged immobilisation (or temporary immobilisation including air travel >4 hours can also be a risk factor), major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma (discontinue use of the pill at least four weeks before elective surgery and not resume until two weeks after complete remobilisation), positive family history (the woman should be referred to a specialist), other medical conditions associated with VTE (cancer, systemic lupus erythematous, haemolytic uraemic syndrome, chronic inflammatory bowel disease such as Chrohn's disease or ulcerative colitis and sickle cell anaemia, increasing age (particularly above 35 years). There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis. The increased risk of thromboembolism in pregnancy and particularly the 6-week period puerperium, must be considered. *Risk of ATE:* Epidemiological studies have associated the use of CHCs with an increased risk for ATE (myocardial infarction) or for cerebrovascular accident (e.g.TIA, stroke). Risk factors for ATE include increasing age particularly if above 35 years, smoking, hypertension, obesity, positive family history, migraine, other medical conditions associated with adverse vascular events such as diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus. Refer to SmPC for symptoms of ATE. Advise patients to seek urgent medical attention if experiencing possible symptoms of thrombosis. *Tumours:* An increased risk of cervical cancer in long-term users of COCs (> 5 years) has been reported. A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. *Other conditions:* Women with or a family history of hypertriglyceridaemia may be at an increased risk of pancreatitis when using COCs. Although small, increases in blood pressure have been reported with COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then withdraw the COC and treat thehypertension. In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs. Diabetic women should be carefully observed while taking COCs, particularly in the early stage of COC use. Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use. Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs. Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. This medicinal product contains not more than 50 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration. **Interaction with other medicinal products and other forms of interaction:** Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure. *Management:* Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks. Short-term treatment: Women on treatment with enzyme- inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation. Long-term treatment: In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended. *Substances increasing COC clearance:* Barbiturates, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum). *Substances with variable effects on COC clearance:* When co-administered with COCs, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. *Substances decreasing COC clearance:* Concomitant administration of strong CYP3A4 inhibitors (such as ketoconazole and erythromycin) can increase plasma concentrations of the estrogen or the progestin or both. Oral contraceptives may affect the metabolism of certain other active substances; plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine). The use of contraceptive steroids may influence the results of certain laboratory tests. **Fertility, pregnancy and lactation**: *Pregnancy:* Qlaira should not be used during pregnancy, withdraw immediately if pregnancy occurs. *Lactation:* The use of COCs is not recommended. **Undesirable effects:** *Common side effects*: headache, abdominal pain, nausea, acne, amenorrhea, breast discomfort, dysmenorrhoea, intracyclic bleeding (metrorrhagia), weight increased. *Uncommon side effects:* fungal infections, vulvovaginal mycotic infection, vaginal infection, increased appetite, depression/depressed mood, emotional disorder, insomnia, libido decreased, mental disorder, mood change, dizziness, migraine, hot flush, hypertension, diarrhea, vomiting, liver enzymes increased, alopecia, hyperhidrosis, pruritus, rash, muscle spasms, breast enlargement, breast mass, cervical dysplasia, dysfunctional uterine bleeding, dyspareunia, fibrocystic breast disease, menorrhagia, menstrual disorder, ovarian cyst, pelvic pain, premenstrual syndrome, uterine leiomyoma, uterine spasm, uterine/vaginal bleeding incl. spotting, vaginal discharge, vulvovaginal dryness, fatigue, irritability, oedema, weight decreased, blood pressure changes. *Rare side effects:* candidiasis, oral herpes, pelvic inflammatory disease, presumed ocular histoplasmosis syndrome, tinea versicolor, urinary tract infection, vaginitis bacterial, fluid retention, hypertriglyceridaemia, aggression, anxiety, dysphoria, libido increased, nervousness, nightmare, restlessness, sleep disorder, stress, disturbance in attention, paraesthesia, vertigo, contact lens intolerance, dry eye, eye swelling, myocardial infraction, palpitations, bleeding varicose veins, VTE, ATE, hypotension, phlebitis superficialis, vein pain, constipation, dry mouth, dyspepsia, gastrooesophageal reflux disease, focal nodular hyperplasia of the liver, cholecystitis chronic, allergic skin reaction, chloasma, dermatitis, hirsutism, hypertrichosis, neurodermatitis, pigmentation disorder, seborrhea, skin disorder, back pain, pain in jaw, sensation of heaviness, urinary tract pain, abnormal withdrawal bleeding, benign breast neoplasm, breast cancer in situ, breast cyst, breast discharge, cervical polyp, cervix erythema, coital bleeding, galactorrhea, genital hemorrhage, hypomenorrhoea, menstruation delayed, ovarian cyst ruptured, vaginal odour, vulvovaginal burning sensation, vulvovaginal discomfort, lymphadenopathy, asthma, dyspnoea, epistaxis, chest pain, malaise, pyrexia, smear cervix abnormal. **Marketing Authorisation Holder**: Bayer Limited, The Atrium, Blackthorn Road, Dublin 18. **MA Number:** MA639/02701 **Further information available from:** Alfred Gera and Sons Ltd. Qormi **Tel**: 21446205 **Classification for Sale or Supply:** Prescription only. **Date of preparation**:04/2019

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TAMARA ATTARD MALLIA, DR EDITH SAID

Neuropsychosocial Outcomes

of Patients With Untreated Craniosynostosis

ABSTRACT

Objective: To review research of visual, auditory and cognitive deficits alongside psychological impacts on patients with untreated craniosynostosis.

Methods: A 26-reference review from Pubmedallowed us to compile outcomes according to their experimental research.

Results: Auditory difficulties which have been identified, mainly in syndromic craniosynostosis were otitis media and deafness. Visual pathologies included exorbitism, astigmatism and strabismus, mostly in syndromic craniosynostosis. Cognitive deficits effect attention span, acedemic performance, memory and language. Lack of autonomy and inability to connect with others are few of the many psychological impacts that were found to correlate with craniosynostosis.

Conclusion: Future research should increase control groups of unaffected children and sampling sizes. This enables better comparison with more accurate mean values and thus any significant or insignificant deviances can be accounted for properly. Routine neuropsychological testing on such patients is recommended.

Keywords: Craniosynostosis, Complications, Untreated, Neuropsychosocial, Cognitive

1.0 INTRODUCTION

Craniosynostosis is the premature fusion of one or more sutures of the skull, namely metopic, lambdoid, sagittal and coronal sutures. It can present as an isolated deformity or as part of a syndrome. Pfeiffer, apert, crouzon, muenke and saethre-chotzen syndromes are the more common conditions that craniosynostosis manifests in.[1] Causes are mainly genetic, especially the syndromic forms, and the phenotype severity differs from mild to very severe. Namely, sagittal and metopic synostosis usually present with one clinical feature, a palpable bony ridge.[1] This creates a dilemma for parents in view of the risks associated with misdiagnosis as well as the risks of craniosynostosis being left untreated. If the parents or the patient never consent to treatment as the options may prove too difficult to decide upon, craniosynostosis may be left untreated. As a result, the raised intra-cranial pressure (ICP) leads to visual pathologies, auditory impairments and cognitive deficits.[2] All of these have a significant impact on thechild psychologically.

1.1 AUDITORY IMPAIRMENTS

Patients with craniosynostosis may have difficulty with audio, leading to disordered communication. Hearing loss mainly occurs in syndromic craniosynostosis, 91% of which is due to an FGFR-2 gene mutation.[3,4] As a result, speech is usually also impaired because word articulation proves difficult. This leads to a prolonged I-to-III interpeak latency of the auditory brainstem's response, which in turn form an abnormal wave II.[3] As shown in figure 1.1, anatomically, this pathology is probably due to raised ICP that compresses the auditory nerve as it is passing through the internal auditory meatus via the internal auditory canal.[3]

Associated complications included 27% that lost their hearing and all suffered from recurrent otitis media.[1,3,4] As shown in figure 1.2, this is recurrent inflammation of the middle ear treated by effusion. Assistive devices and sign-language can help such children to lead as much of a normal life as possible.

1.2 VISUAL PATHOLOGIES

The orbital area may be compromised as a result of craniosynostotic facial deformities which in turn lead to optic pathologies.

1.2.1 Exorbitism

The orbital area may be reduced due to the facial deformities present resulting in exorbitism. As shown in figure 1.3, the eyes of such patients protrude outwards; most commonly in patients with crouzon or apert syndrome.[1,7] Patients are more susceptible to corneal injury, infection or ulcers due to the upper eyelid being unable to protect the eyeball itself.[7]

1.2.2 Astigmatism and Strabismus

In syndromic craniosynostosis, the most commonly associated visual morbities are astigmatism and strabismus.[1] In isolated craniosynostosis, patientsare more susceptible to developing astigmatism in the eye contralateral of the fused suture.[1] Astigmatism is an abnormal curvature of the lens, leading to blurred vision as shown in figure 1.4. Patients present with a less spherical lens which results in an inability for light rays to meet at a common focus, thus forming a distorted image. Corrective surgery or lenses usually help these patients see clearer.[9]

The raised ICP may compress occular areas of the brain which in turn may lead to misaligned eyes known as strabsimus. As shown in figure 1.5, this varies according to the direction of misalignment. As a result, patients develop amblyopia (lazy eye) where the brain fails to process inputs from the effected eye and starts to favour the other. Vision weakens and tends to get worse if not aided by glasses, prisms, eye exercises or corrective eye muscle surgery.[11]

1.3 COGNITIVE DEFICITS

Older research has focused poorly on such cognitive outcomes as these lacked standard tests, control subjects and appropriate follow-up assesments. Currently, the Bayley Scales of Infant Development and the Wechsler Intelligent Scales of Children have looked upon mental deficits, not only in syndromic craniosynostosis but also in isolated forms.[1] Figure 1.6 explains how the patient's development is classified. Patients with single-suture craniosynostosis, such as unicoronal or unilambdoid synostosis, carry a

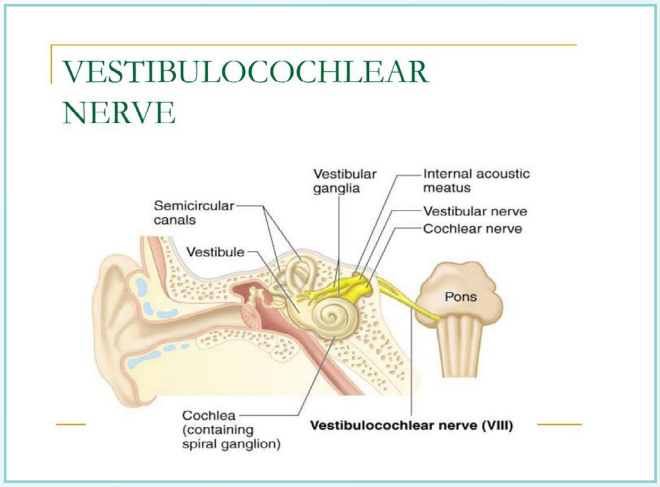

Figure 1.1: Passage of the auditory nerve (vestibular nerve & cochlear nerve)[5]

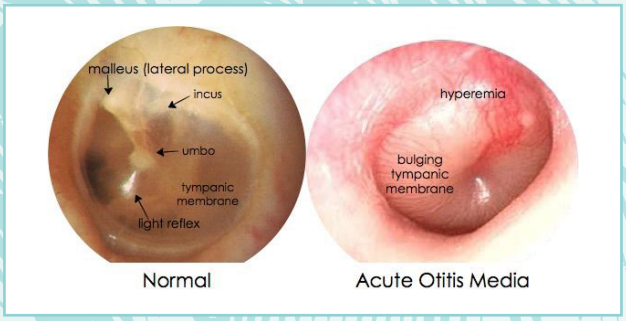

Figure 1.2: Normal Ear (left) and Acute Otitis Media (right)[6]

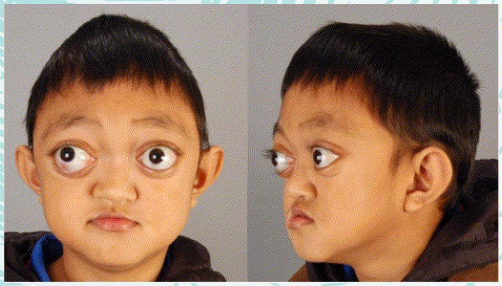

Figure 1.3: Seven year-old male with Crouzon Syndrome presents with exorbitism[8]

three to five-fold increased risk for such deficits.[13] Knight et al. proposed a systematic review in 2014 of 33 documents with special focus on methodology.[14] As a result, ten studies showed mental retardation, including language. Five studies of children averaging nine years old, showed normal IQ levels but three others showed increased learning disability and memory loss.[15,16] Cognitive imagery, attention span and acedemic performance were also recorded to be in deficit with patients of untreated craniosynostosis. Evidently, many assumptions with little research to back it up is present since many studies have contradicted each other.[17] However, in totality it can be concluded that some correlation between cognitive deficit and raised ICP exists.[17]

1.4 PSYCHOLOGICAL IMPACTS

The previous complications alongside the day-to-day challenges every person faces, leave a child with craniosynostosis conflicted and relatives in need of support in order to enable an easier life for their child. Along the stages of development, the family is confronted with ongoing medical decisions that need to be taken and psychological difficulties that need to be dealt with.[19]

1.4.1 Infant to School Age

During infanthood, the crucial psychosocial burden lies with the parents as they need to learn, adapt and manage their child's needs. Specifically in children with syndromic craniosynostosis, parents would have to deal with others' antipathetic reactions and be conflicted to choose their child's schooling. The child's appearance will also leave the parents confronted with dismissal from other parents thus, preventing child-to-child relationships.[1]

Once the child has begun to attend school, the challenges are posed more on the child rather than the parents alone. As a result, these children may find it difficult to make friends as they are dismissed. Furthermore, their reduced cognitive and motor skills may hinder them from participating in activites and academics, leaving these children at a disadvantage.

1.4.1.1 Medical Complications

Despite treatment, these children may still suffer from complications and unfortunately require hospitalisation. Approximately 10% of children admitted to the intensive care unit have experienced post-traumatic stress disorders (PTSD).[20] Parental stress and visibly reduced coping ability have been correlated strongly with PTSD in the child. Indicatively, the stress related to self-image, trauma, cognitive and motor deficits should not only be addressed and treated with the child, but also within the whole family.[1]

1.4.1.2 Abnormal Behaviour

The Child Behaviour Checklist has been used in a recent study by Becker et al. that reported significantly differing behaviour between craniosynostotic and uneffected people.[21] On the other hand, Vlugt et al. found no correlation as such when accounting for IQ.[22] Other studies taken during school age found that 33% of children with non-syndromic trigonocephaly, required a school psychologist. Approximately, 47% required remedial classes, 20% required special needs allowances and 37% were diagnosed with attention deficit disorder, autism and hyperactivity.[23]

1.4.2 Adolescense

In adolescense, approximately one third of patients have experienced bullying pertaining to stigma and appearance.[19] Most patients cope with continuous support and social interventions. Moreover, they are confronted with difficulty to be autonomous as they begin to reach adulthood and are required to consent and plan their own health-care with their specialists. It is emphasised that these patients should realistically form treatment expectations.[1]

1.4.3 Adulthood

Unfortunately, there have been little to no studies regarding non-syndromic craniosynostosis. Adults with Apert and Crouzon syndromes had a lower acedemic level, were less often married, experienced less sexual connections and had depressive mood periods.[24,25] However, they were just as likely to report a positive outlook on life in general. Indicatively, adults who experienced such depression were willing to undergo corrective surgery in adulthood despite the increased risks and complications.[26]

1.5 CONCLUSION

Indicatively, there are many ramifications that can occur if craniosynostosis patients are left untreated. In Malta, craniosynostosis is significantly rare with an average of two cases yearly from 1993 to 2016. The highest being 5 cases in 2011, all of which were live births. From a total of 28 cases in 24 years, only one fetal death in 1996 was reported. As a result, the total prevalance report as at 2016, was 2.71%.[27] The neuropsychosocial outcomes were highlighted in this review however, there are many others such as physiological and motor complications that were not mentioned

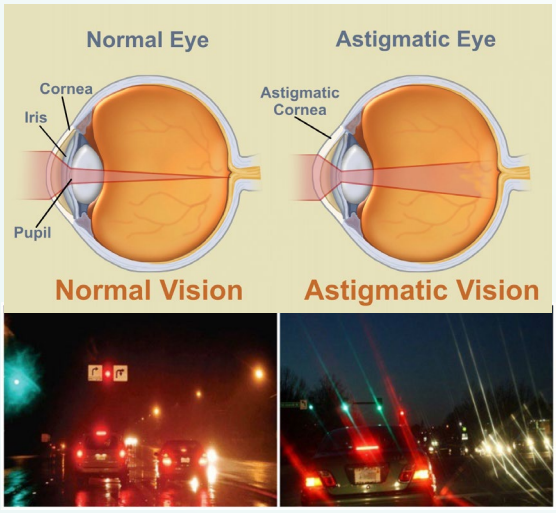

Figure 1.4: Normal vision meeting at a common focus (top left). Clear images during the night (bottom left). Astigmatic vision lacking a common focus (top right). Distorted images during the night (bottom right). Adapted from Health Jade[10]

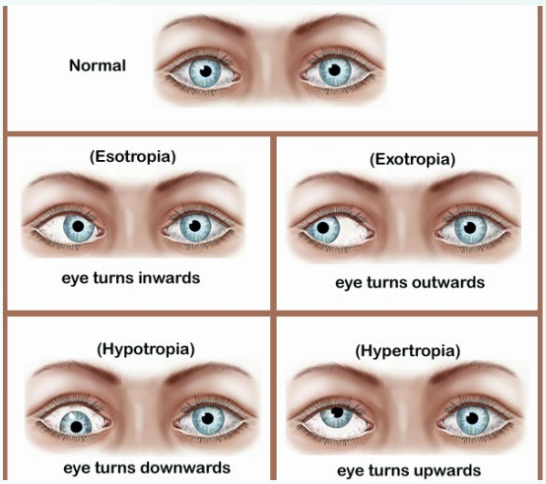

Figure 1.5: The different types of strabismus in comparison to the normal condition.[12]

in this review. It was deemed appropriate to focus on the cognitive and pyschological aspects as there is less insight on these topics as such. The visual and auditory impairments leave a child unable to communicate. The abnormal cognition leaves a child confused and struggling to make sense of things that others are thriving upon. All this with the added societal pressure and parental stresses leave a significant impact on the child's development, behaviour and his or her future relationships. This research has enabled a general review of all the possible long-term outcomes the patient may be confronted with. This emphasises the strong requirement of a well-explained set of facts to the patient so as to make the best decisions regarding their health care plan in a multi-disciplinary approach.

ACKNOWLEDGEMENTS

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Personally, I would like to thank my family, friends and fellow medical students for their consistent encouragement.

Classification	Equivalent BSID-III Scaled Scores	Definition
At risk	1-4	Child is most likely in need of further evaluation to determine need for early intervention.
Emerging	5-7	Child has some risk for developmental delay, but further evaluation is made on the basis of other information collected. Can monitor develop or refer for further evaluation.
Competent	8-19	Child is considered at low risk for developmental delay and in most cases does not need further evaluation.

Abbreviation: BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition.

Figure 1.6: Bayley Scales of Infant Development[18]

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DR ALEX CARACHI

Urinary Incontinence and Urodynamics

The incidence of urinary incontinence (UI) is on the increase worldwide, prevailing mostly among women (25-45%) but also affecting men (1-9%). Over the past years awareness on this condition has been on the rise and more patients have been willing to disclose their complaints and seek medical advice in order to combat, more effectively, a disorder which causes significant morbidity, both physically and psychologically. Multiple studies have shown that quality of life is poorer in patients suffering from UI and in some, it may be a marker of poor health status, especially in the elderly population.

The aetiologies of UI are multiple and can be transient or long-standing. The incidence increases with age, parity, history of pelvic surgery, smoking, increased BMI, menopause, diabetes mellitus, caffeine/alcohol intake, as well as cognitive and functional impairment. Initial investigations aim at identifying causes for lower urinary tract symptoms (LUTS) – which include UI symptoms namely stress UI; urgency UI; mixed UI; nocturnal enuresis; postural incontinence; continuous, insensible and coital incontinence – and other conditions affecting the bladder and urethra.

A thorough history is taken in order to evaluate and identify the source of the client's complaint followed by a physical examination of the cardiorespiratory, neurological and gastrointestinal systems. In women a pelvic examination is performed to rule out organ prolapse or lower tract pathology and in males a digital rectal examination, in order to rule out prostate pathology. The patient is assessed for storage and voiding symptoms and any suspicious signs, such as haematuria, bacteriuria and dysuria are addressed with appropriate investigations including urine microscopy, sensitivity and cytology, imaging and endoscopy accordingly.

Most patients suffering from UI are treated according to their symptoms, history and clinical examination - after any other possible pathology has been ruled out. These treatments mainly include behavioural therapy such as bladder training and pelvic floor physiotherapy, anti-muscarinics and other pharmacological treatments including alpha-blockers and 5-alpha-reductase-inhibitors. However, cases can be more complex and the latter investigations and treatments might prove insufficient.

The International Continence Society (ICS) suggests further assessment through internationally validated tools, including bladder diaries and questionnaires which aid in assessing more closely the clients' symptom frequency and severity, also providing a baseline for evaluating the condition after treatment. Some of these tools assist the clinician in evaluating the impact of the patients' complaints on the quality of life, sexual and social function. Furthermore, these questionnaires, help the clinician better identify the possible need for more specific investigations, such as Urodynamics.

Urodynamics incorporates a set of tests which are carried out as an adjunct to clinical diagnosis in order to support the latter with objective measurements that can be reproduced and quantifiable. One of the main aims of urodynamics is that of identifying and measuring the complaints of the patients and thus providing a pathophysiological rationale for their symptoms, whilst corroborating them with the urodynamic findings.

Complex cases which fail to be resolved with non-invasive measures require further investigations. The latter are also indicated in those patients which have already undergone previous surgery, especially if related to their symptoms and even in those patients, for whom surgery might be potentially complicated. In the past, procedures done for LUTS/UI were mainly based on LUTS, however, over the last decades, the use of Urodynamics has showed that most of the symptoms were of poor diagnostic value and at times, the surgery yielded no clinical benefit.

Urodynamic studies encompass an array of tests that vary in complexity. Uroflowmetry together with voiding assessment can be used in conjunction with ultrasonography. This is a non-invasive test that can help identify a voiding pathology and can also be used as a follow-up to assess response to treatment or to plan for possible more invasive treatment options.

Pressure studies, which include cystometry, provide information on the patient's bladder filling function. It is another test which is used to assess storage symptoms in various types of UI whilst aiding to distinguish the latter from overactive bladder (OAB) symptoms. In conjunction with flow studies, these tests help to distinguish between intrinsic bladder pathologies such as underactive detrusor (UD) muscle or bladder outlet obstruction (BOO). Thus, these tests reproduce and record the coordination between the urinary bladder detrusor muscle and the urethra or pelvic floor during the voiding phase. Furthermore, if there is the need to assess the anatomy together with the function of the lower urinary tract, video-urodynamics can be utilized for such an assessment.

Other possible tests which can be offered at Urodynamics are Electromyography (EMG) studies, which reflect the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter and the striated pelvic floor muscles. Lastly, urethral pressures can also be evaluated, an investigation which is selectively used in neuro-urological cases.

Nowadays, with the aid of novel investigations and a better understanding of the functional physiology of the lower urinary tract, UI can be better understood and better treated. The urinary bladder, which was once considered as an "unreliable witness", has become, with the aid of medical advances, a precious ally.

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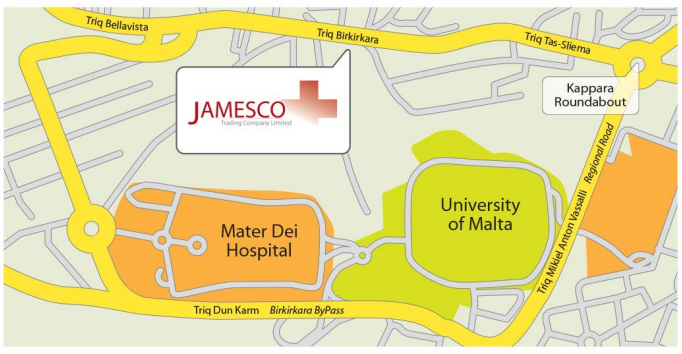

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DR PIERRE VASSALLO

Imaging Back Pain
Part 3

This is the third and last article about imaging back pain. The first article presented the mechanisms of discogenic back pain. This second one discussed osseous causes of back pain. This article will cover miscellaneous causes of back pain including osteoradionecrosis and insufficiency fractures, bone infarcts, traumatic fractures, facet joint disease, myofascial and paravertebral causes and spinal instability issues.[1]

OSTEORADIONECROSIS AND INSUFFICIENCY FRACTURES

Osteoradionecrosis results from exposure of bone to radiotherapy, which is used to treat bone metastases. Radiotherapy induces necrosis in bone metastases, which is followed by bony sclerosis that strengthens the bone thereby reducing risk of fractures secondary to metastatic disease.

Radiotherapy also causes a replacement of the haemopoietic elements in the bone marrow with fat. This is seen as an area of high signal intensity on T1-weighted MR scans and intermediate signal on T2-weighted MRI scans in the region that was exposed to radiotherapy (Fig 1).

Osteoradionecrosis is a severe delayed radiation-induced complication and is characterized by bone necrosis, which shows hypointensity at T1-weighted and hyperintensity at T2-weighted MR scans, with heterogeneous enhancement on administration of contrast material (Fig 2). This bone necrosis leads to insufficiency fractures.

Osteoradionecrosis results in cell necrosis, compromise of the endplates and insufficiency fractures that induce the release of inflammatory cytokines and stimulate neovascularity and neurogenesis all of which cause pain. This may be treated by surgical debridement, hyperbaric oxygen therapy and NSAIDS.

BONE INFARCTION

Bone infarction may be a consequence of many conditions that lead to vascular occlusion; these may include any form of vasculitis, autoimmune disease, sickle cell disease,

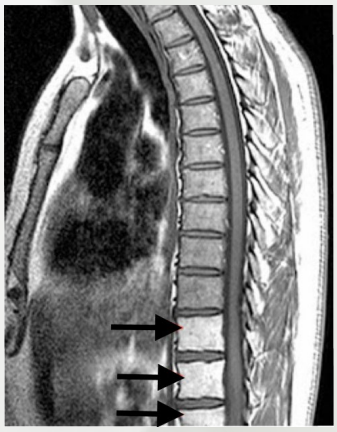

Figure 1: Sagittal MRI scan through the lower thoracic and upper lumbar spine showing high T1 signal in the lower three vertebral bodies following exposure to radiotherapy.

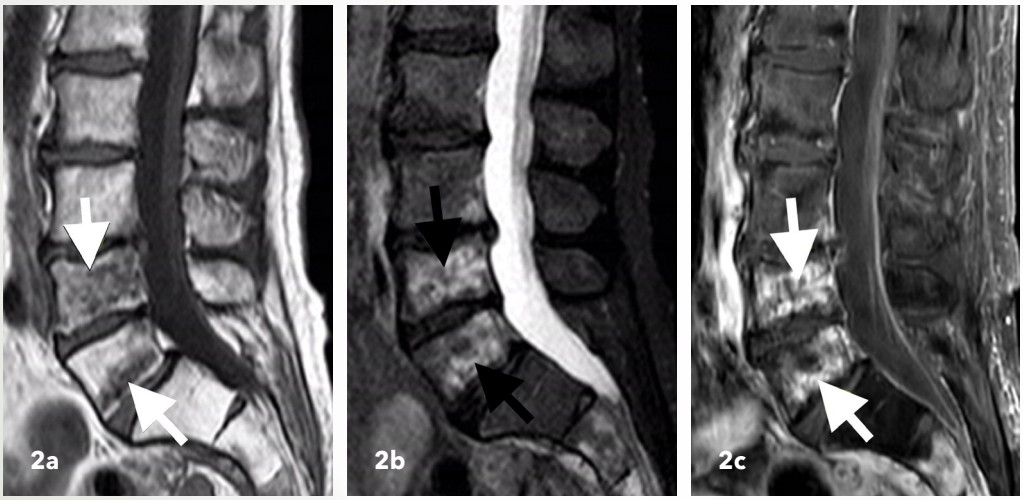

Figure 2: Sagittal scans through the lumbar spine in a patient who had radiotherapy for rectal cancer 5 years earlier show low signal intensity foci on T1-w scans (a) that represent fractures in L4 and L5 vertebral bodies. High signal foci on T2-w scans (b) correlate with areas of osteonecrosis, which enhance on contrast-enhanced T1-w scans (c).

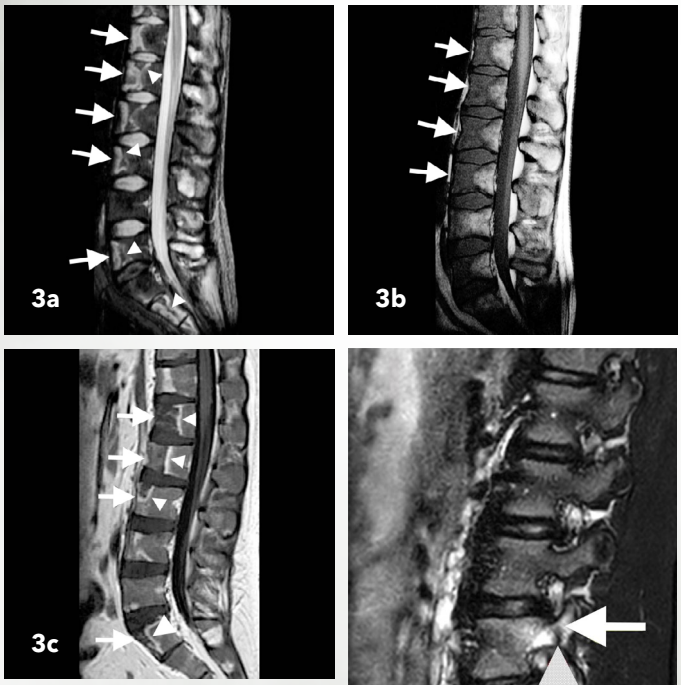

Figure 3: a. Sagittal T2-w MRI scan of the lumbar spine and sacrum showing multiple areas of high signal in the anterior portions of T11 to L4 vertebral bodies, L5 and the sacrum (arrows). Note that there is some suggestion of a double line sign in some of the bone infracts (arrowheads). b. Sagittal T1-w MRI scan of the same area shows low signal in the infarcted areas (arrows) due to replacement of fatty marrow by oedema. c. The contrast-enhanced T1-w scan shows rim enhancement (arrowheads) of the infarcts corresponding with the areas of neovascularity.

Figure 4: Sagittal STIR MR image showing a pedicular fracture as a low signal intensity line (curved arrow) with adjacent vertebral oedema that extends into the superior articular process (straight arrow).

thalassaemia and corticosteroid therapy.[2] It is also seen on acute lymphocytic leukaemia and may be consequent to the malignancy itself or to treatment with corticosteroid. Bone infarction may be the first indicator of systemic disease.

Hypoxia leads to bone necrosis and invasion by macrophages, which produce pro-inflammatory cytokines that cause tissue inflammation. Sensitisation of nociceptors located in the bone marrow and periosteum to inflammatory cytokines results in pain.

Infarct bone appears as having low signal on T1-weighted images and high signal on T2-weighted images. Occasionally, high signal may be present on T1-w images due to accumulation of protein-rich fluid. Contrast enhancement is present in areas of neovascularity (Fig 3). A double line sign is pathognomonic of bone infarction but is more frequently evident in the long bones: this correlates with adjacent layers of granulation tissue (high T2 signal) and bony sclerosis (low T2 signal) at the margins of a bone infarct.

Vertebral infarction mainly involves the anterior portions of the vertebral bodies and is rarely seen in the posterior elements.

VERTEBRAL FRACTURES

Vertebral fractures are frequently primary and result of trauma. However, they may also be secondary to metastatic disease, osteoporosis and osteonecrosis.

Fractures are best seen on STIR or heavily T2-weighted MR scans, where the fracture appears as linear low signal intensity and adjacent bone shows high T2 signal due to bone marrow oedema (Fig 4). Vertebral body deformity is seen in case of a burst or wedge fracture.

Neovascularity that occurs as part of the healing process causes an inflammatory response with the release of tumour necrosis factor (TNF) and interleukin 1β; both inflammatory mediators stimulate nociceptors in the bone marrow and periosteum that lead to pain. This is treated with NSAIDS and rest.

FACETOGENIC PAIN

The facet joints are synovial joints between the superior and inferior articular processes of adjacent vertebrae. They are prone to all types of inflammatory and degenerative disease processes as other synovial joints. The articular cartilage, synovial membrane, joint capsule and the subchondral bone contain proprioceptive and nociceptive nerve endings that transmit pain stimuli to the segmental nerves.

Facet joints receive dual innervation from two adjacent segmental nerves; thus, the L4/5 facet joint receives its innervation from the descending medial branch of L3 dorsal ramus and the ascending medial branch of L4 dorsal ramus.[3] Hence, pain originating from a facet joint is felt at two segmental levels, and any pain relief treatment (such as radiofrequency nerve ablation) will need to address both levels to be effective.[4]

Facet joint arthropathy is known to account for 30% of chronic low back pain. It is due to degenerative change that leads to hypertrophy of the facet joints. Hypertrophy of the facet joints is seen as joint enlargement with osteophytes, which may encroach on the adjacent neural foramen and cause segmental nerve root impingement. Increased fluid within the synovial joint is also seen (Fig 5). These changes in the facet joint have been shown to be induced by mechanical loading of the back and repetitive trauma. Hyperextension, rotation and lateral flexion usually increase pain. However, there is poor correlation between the extent of facet joint arthropathy and severity of back pain.

Interleukin 1β has been shown to leak out of hypertrophic facet joints and to stimulate nociceptors related to the adjacent segmental nerve.

Treatment options vary from NSAIDs to surgical decompression in case of neurological impingement. Radiofrequency ablation, cryoablation or chemical neurolysis with phenol or alcohol may be used to block pain originating within the facet joint.

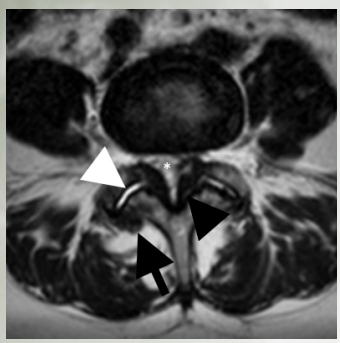

Figure 5: Transverse T2-w scan through L4/5 facet joints shows fluid in the joint cavity (white arrowhead), hypertrophy of the capsule with osteophyte formation (black arrow) and hypertrophy of the ligamenta flava (black arrowhead). Capsular hypertrophy may encroach on the neural foramen and cause segmental radicular pain. Hypertrophy of the ligamenta flava may result in spinal canal stenosis as seen in the case (*).

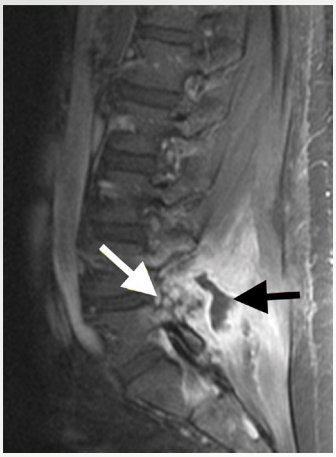

Figure 6: Sagittal contrast enhanced T1-w scan shows enhancement in L4/5 facet joint (white arrow) and a peripherally enhancing abscess cavity (black arrow) in the paraspinal tissues. There is no enhancement with the pus-containing portion of the abscess since this is avascular.

FACET JOINT INFECTION

Facet joint infections result from haematogenous spread of infection after bacteraemia. Facet joint infections may be accompanied by epidural (25% of cases) or paraspinal abscesses; these abscesses are seen as areas of diffusion restriction on Diffuse Weighted Imaging MR scans and show peripheral enhancement on contrast-enhanced MR scans (Fig 6).

Contrast-enhancement helps to distinguish infectious from degenerative joint disease, since the latter contrast-enhancement is minimal.[5]

The presence of infection results in inflammation with the release of pro-inflammatory cytokines such as TNF and Interleukin with stimulate the capsular and adjacent nociceptor and result in local pain. Treatment includes systemic antibiotics and surgical debridement is often required.

SPINAL INSTABILITY

Any damage to joints or soft tissues that are responsible for maintaining alignment of the spine can lead to spinal instability. Spinal instability is a state in which more movement is allowed than is under normal circumstances in a stable spine. This abnormal / increased movement results in further damage to the spinal joints. Through various mechanisms including fibrosis, bony sclerosis and new bone formation, the spine attempts to limit these abnormal movements and to restore stability. These restorative mechanisms limit vertebral slippage (spondylolisthesis) but also limit physiological movement.

The cyclical process of joint/soft tissue damage, destabilisation and re-stabilisation may continue and may result in chronic back pain. In the early stages, imaging findings may be absent. However, disk and facet joint findings become evident in the later stages.

Procedures to stabilize the spine should hypothetically prevent progressive tissue and joint damage and limit pain. However, there appear to be poor correlation between abnormal spine mobility and pain. There is better correlation between abnormal load distribution and pain.[6]

MYOFASCIAL AND PARASPINAL PAIN

Myofascial pain has been shown to affect up to 85% of the general population at some time during their lifetime. It is caused by myofascial trigger points that are identified by means of palpation as foci of hypercontracted areas in a muscle. These result of muscle overuse or trauma, but may also result from psychologic stress.

The sustained contractile activity and cell stress occurring at myofascial trigger points induce the increased release of myokines, inflammatory cytokines, and neurotransmitters that contribute to the accentuation of the same myofascial trigger points and to myofascial pain syndrome.[7]

Tendinopathy of the paraspinal muscles, the clinical syndrome of pain and dysfunction in a tendon, is often a chronic condition. Symptoms of tendinopathy include localized tendon pain with loading, tenderness on palpation, and impaired function. Tendon pain has a transient intermittent nature that is closely linked to loading. Many biochemical changes occur in patients with tendinopathy. Tendon pain is likely mediated by proinflammatory cytokines that stimulate local nociceptors.

Myofascial pain and tendinopathy are rarely associated with any imaging findings and must often be identified based on clinical examination alone.

CONCLUSION

Low back pain presents a broad clinical and diagnostic problem for patients, physicians, and radiologists. This article and the previous two have attempted to demonstrate the most common causes of low back pain and to discuss diagnostic and treatment options.

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To **all members of our team** who worked hard to adapt and find new ways to nurture TheSynapse, CME30.eu and all members in spite of all challenges of 2020.

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