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thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

ChatGPT:
A Game-Changer for Society

Audit of Pain Management in Trauma Surgery at MDH

Family Businesses Time to Shape up!

Minimal Access Surgery in Gynaecology

US Imaging of Groin Hernias

ENTRESTO®(sacubitril/valsartan)

Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex).

Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

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 pregn,inc:y.

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/valsartan is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m²). There is no experience in patients with end-stage renal disease and use of 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/valsartan immediately 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 Tu.: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B: type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate. Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan tre,itment should be considered

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 coadministered 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/valsartan is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. 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 C_{max} 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 C_{max} 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; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets.

Legal classification: POM.

Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872.

REFERENCES: 1. Maddox TM, Januzzi JL Jr, Allen LA, et al. 2021 update to the 2017 ACC Expert Consensus Decision Pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772–810. 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-related 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 June 2021.

2021-MT-ENT-19-MAY-2021

ENT AD1 03/23 MT

NOVARTIS

Entresto® sacubitril/valsartan

LOWER. LONGER.
LEQVIO®[1].

TWO DOSES A YEAR[1*]

*LEQVIO is dosed initially, again at 3 months, and then once every 6 months.[1]

EFFECTIVE AND SUSTAINED LDL-C REDUCTION[1†]

†LDL-C reduction was maintained during each 6-month dosing interval.[1]

Choose LEQVIO first for effective and sustained LDL-C reduction and as a strong complement to a maximally tolerated statin for your patients with ASCVD.[1]

LEQVIO®

PRESENTATION: Leqvio 284 mg solution for injection in prefilled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. ♦*Missed doses*: If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. ♦*Treatment transition from monoclonal antibody PCSK9 inhibitors*: Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. ♦*Elderly, hepatic impairment, renal impairment*: no dose adjustment is necessary. Inclisiran should be used with caution in patients with hepatic and renal impairment. ♦*Paediatric population*: The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. ♦*Method of administration*: Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: ♦*Haemodialysis*: The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. ♦*Sodium content*: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

PREGNANCY, LACTATION AND FERTILITY: ♦There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. ♦It is unknown whether inclisiran is excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. ♦No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: *Common*: Adverse reactions at the injection site.

LEGAL CATEGORY: POM PACK SIZES: Pre-filled syringe: x1 pre-filled syringe. Pre-filled syringe with needle guard: x1 prefilled syringe with needle guard.

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

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001-2

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

2022-MT-LEQ-24-MAR-2022

References: 1. Novartis Europharm Ltd. Leqvio Summary of Product Characteristics.

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LEQVIO® inclisiran

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5 Classes

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Session 3	Cardiometabolic problems in men Dr Mark Abela
Session 4	Low T and other hormonal issues in Men Dr Mario Cachia
Session 5	Men and GU Problems Dr Donia Gamoudi
Webinar	Opportunistic Screening in Men
Planned Date	To be Announced Soon

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Issue Guide

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'**Creation**'
This underwater image shows camouflage groupers (Epinephelus polyphekadion), emerging from a cloud of eggs and sperm in Fakarava, French Polynesia, in the South Pacific Ocean. This is a species vulnerable to extinction. This event takes place each July around a full moon. The photo won the top prize at Wildlife Photographer of the Year 2021.

octenisept®

Antiseptic solution for wounds and mucous membranes

Octenidine hydrochloride (1 mg/mL) and phenoxyethanol (20 mg/mL)

A newer approach to infection control in wound care

Features

- Broad spectrum antiseptic including Multidrug-Resistant Organisms[1]
- Favorable biocompatibility index[2]
- Once daily application
- Fast acting (1 minute)
- Non – stinging
- Alcohol-free
- Colourless
- Efficacy not compromised in presence of organic material[3]
- Suitable for use on adults and children

Application:

octenisept® is used for the short-term antiseptic preparation of mucous membranes and the surrounding skin before diagnostic and surgical procedures on reproductive or excretory organs, including the insertion of a urinary catheter; suitable for repeated use;

Repeated short-term antiseptic treatment of small superficial wounds and for facilitating the healing of the wound. The medicine can be used in all age groups.

Direction for use:

octenisept® is applied onto the area to be treated once per day, completely moistening the area with the medicine.

Caution:

Octenidine-based products ARE NOT recommended for use on exposed cartilage, in the abdomen (e.g. during surgery), middle ear, in the urinary bladder or other enclosed spaces.

Do not use if you are allergic to Octenidine Hydrochloride, Phenoxyethanol or any of the other ingredients.

octenisept® is not to be applied under pressure (by using a syringe). Where applicable ensure adequate drainage of the wound cavity (by using a flexible drainage tube).

Do not use on eyes.

For the latest copy of the approved Summary of Product Characteristics please access our website *https://www.premierehealthcare.com.mt/octenisept*

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1. Amalaradjou, M. and Venkitanarayanan, K. (2014) "Antibiofilm effect of octenidine hydrochloride on Staphylococcus aureus, MRSA and Vrsa," Pathogens, 3(2), pp. 404–416. Available at: https://doi.org/10.3390/pathogens3020404.

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GUEST EDITORIAL

PROF. ALEXIEI DINGLI
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ChatGPT: The AI Game-Changer Transforming Healthcare and Society

Imagine conversing with an Artificial Intelligence (AI) that can understand you, respond to you, and generate text based on your input. Sounds like science fiction, right? Well, not anymore. Meet ChatGPT, a chatbot developed by OpenAI that can do all that and more.

The company was initially co-funded by Elon Musk as a not-for-profit entity. Today that is no longer the case, and Microsoft is trying to own a significant stake in it. ChatGPT uses an AI technique called Transformers which was invented in 2017. It is built on another model called GPT-3, a large language model trained on hundreds of billions of words from the internet. This model, released in 2020, was already in the news when Elon Musk flagged it as too dangerous for public release. Eventually, Microsoft bought its exclusive license and created Co-Pilot, a tool capable of writing computer programs. But late last year, OpenAI released ChatGPT, an enhanced GPT-3 version which took the world by storm. Essentially, the difference between this and previous versions is that it uses various learning techniques to optimize its performance for dialogue by combining both human and machine supervision in the process. Thanks to this approach, it can produce human-like text in various formats and styles, such as jokes, stories, poems, essays, tweets, code snippets, etc.

ChatGPT has many potential applications in various domains, such as education, research, health care, entertainment, and more. However, it also poses challenges and ethical issues that must be addressed carefully.

One of the challenges is how to use ChatGPT effectively in educational settings. ChatGPT can be a valuable tool for students to learn new concepts, practice their skills, and get feedback from an AI tutor. However, it can also generate inaccurate or misleading information that can confuse or misinform students. Teachers need to educate students to scrutinize the content generated by ChatGPT through digital literacy and critical thinking skills.

Another challenge is how to ensure the safety and reliability of ChatGPT in research and development settings. ChatGPT can help researchers explore new ideas, generate hypotheses, analyze data, and write papers. However, it can also produce harmful or untruthful outputs that can compromise the quality and integrity of scientific work. Researchers need to verify and validate the results generated by ChatGPT using human feedback and other methods.

A third challenge is how to leverage ChatGPT for healthcare settings. ChatGPT can assist doctors in diagnosing infections, prescribing antibiotics, providing advice, and communicating with patients. However, it can offer unsafe or inappropriate advice
that can endanger patients' health or violate privacy. One has to keep in mind that the ultimate scope of this model is to generate an answer and hence, doesn't guarantee the correctness of that response. Thus it is crucial to keep the human element in the loop. Doctors need to supervise any interactions between ChatGPT and patients and intervene when necessary.

Despite these challenges, ChatGPT also offers many opportunities for AI and society. It can enhance human creativity, collaboration, and communication by generating novel, relevant, and engaging texts in various formats or styles. ChatGPT can improve human well-being, productivity, and learning outcomes by providing personalized, adaptive, and supportive feedback in multiple contexts and scenarios. Let's not forget that not everyone is comfortable interacting with a computer. ChatGPT is making natural language exchanges commonplace, thus helping to narrow the existing digital divide.

In conclusion, ChatGPT is a game-changer for AI and society. It has many potential applications in various domains but poses challenges and ethical issues that must be addressed carefully. ChatGPT can generate human-like text in multiple formats and styles, enhancing human creativity, collaboration, and communication. It can also provide personalized, adaptive, and supportive feedback in multiple contexts and scenarios, improving human well-being, productivity, and learning outcomes. However, ChatGPT also has its limitations and risks. It can produce inaccurate or harmful content if not trained with the correct data. It can expose users to unsafe or inappropriate advice or violate their privacy if malicious actors exploit it. It can affect human values, norms, identities, and relationships if it interacts with users in social and cultural settings. Therefore, as users of ChatGPT, we need to be aware of our responsibilities. We must verify and validate ChatGPT's outputs using human feedback and other methods. We must supervise and monitor ChatGPT's interactions with other users and intervene when necessary. We need to understand the power and potential of such a tool if we want to use it for the good of humanity.

DR DAVID BORG, DR CHRISTINE VELLA, MR KURSTEIN SANT

Pain Management in Trauma Surgery

INTRODUCTION

Trauma patients range from healthy children and adults to frail elderly ones. Pain management in the elderly can be challenging as these patients often present with other co-morbidities. Polytrauma patients, delayed admissions, substance abuse and psychological issues may also result in complication of care.

Appropriate pain management is a patient's right. It also helps early healing, reduces chronic pain and can lead to a shorter hospital stay.[1]

Pain relief is based on the WHO analgesic ladder (Figure 1). This helps to prescribe analgesia in a stepwise fashion and in doing so prevents unwanted adverse effects from using strong opioids.

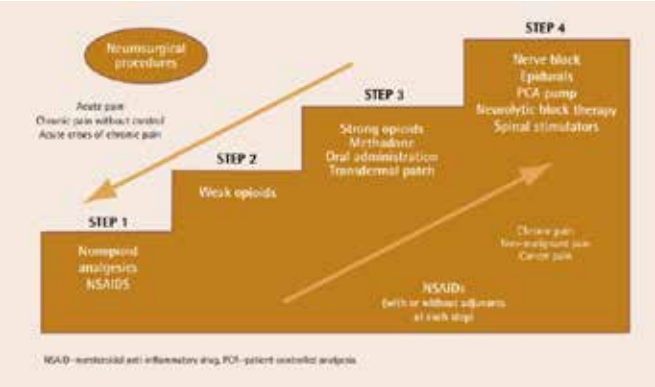


Figure 1. World Health Organization Analgesic Ladder.[2]

BACKGROUND AND AIM

A multitude of patients are admitted to Mater Dei Hospital (MDH) each day in view of fractures and soft tissue trauma. For each trauma admission, the doctor on call should complete a clerking sheet. A section of this clerking sheet includes analgesia prescribed at the time of admission; both for regular and as needed (PRN) analgesia. If analgesia is not prescribed adequately, on call doctors would tend to be contacted at a later stage, in view of patients complaining of pain and without a direct pain control plan. Apart from analgesia, other medications are prescribed, as appropriate, to help mitigate the side-effects of certain analgesics such as laxatives and anti-emetics.

This prospective audit is aimed to study current analgesia prescribing trends in trauma patients admitted at MDH. This audit will therefore attempt to improve the adequacy of analgesia prescribed in new admissions at MDH. Paediatric patients have been excluded.

ETHICS

Before commencing this audit, approvals from the Chairperson of the department of Trauma and Orthopaedics, and the data protection department at MDH (Ref. no. 270A/21) were granted. An audit engagement form as well as a consent form were appropriately devised and handed over to all participants.

METHOD

Treatment charts were reviewed from all trauma admissions (64 patients) over 2 weeks between 20th September 2021 and 2nd October 2021. Table 1 lists the inclusion criteria. Patients ≥ 18 years were included from the MDH online trauma list. Patients which had been diagnosed with liver or renal impairment were excluded. Each patient's blood tests were checked and assessed if a liver profile was taken anytime in the three months preceding admission. If they were deranged according to recommended ranges, the patient has been excluded. If no LFTs were found, the patient's clinical visits were assessed on the hospital's intranet to conclude if the patient was followed up for a liver problem. Also, during data collection, admitting consultants and ward location were kept anonymous. This was important to decrease bias and make the results more reliable.

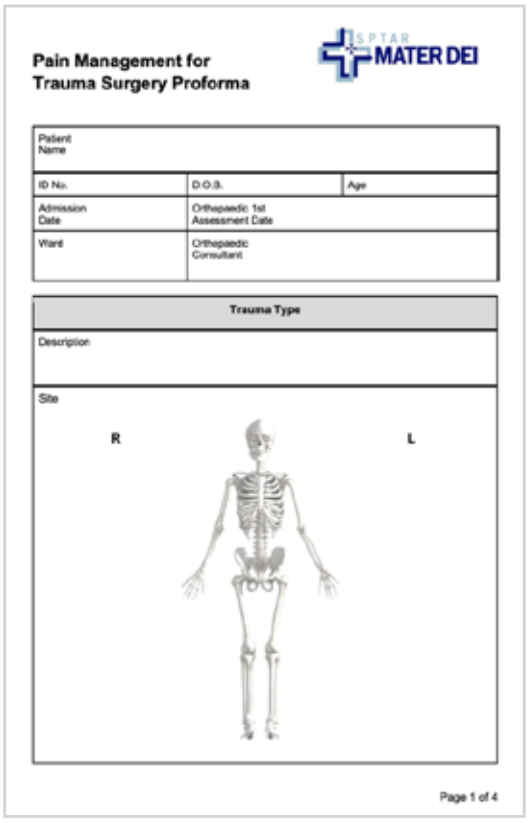
Exclusions
Patients with hepatic or renal impairment: deranged LFTs, C+U in the three months preceding admission
Pregnancy
Patients taking chronic pain control medications

Table 1. Exclusion criteria.

A proforma was prepared (Figure 2) to aid in data collection following a comprehensive literature review. This included patients' details, type and mechanism of injury and operative management – if not treated conservatively. Each patient was also asked to score the level of pain felt pre-operatively and post-operatively using a suitable numerical pain score scale (Table 2) which was adopted from MDH's Anaesthesia department. It was decided that day 1 post op was to be taken for each patient to minimise the differences between patients as some may have been discharged after day 1. Apart from this score, the participants were asked if the analgesia prescribed was enough to control the pain. These 2 questions were asked to each patient every day until day of discharge. All analgesia prescribed pre-operatively and post-operatively along with any updates throughout their admission were recorded on this same proforma. During data collection, to include further post-operative days, page 4 of the proforma was re-printed, and dates filled in accordingly.

Pain score out of 10	Description of the pain
0	No pain
2-3	Mild
4-5	Moderate
6-7	Severe
7+	Extreme

Table 2. Pain Score Scale.



Pain Management for Trauma Surgery Proforma

HOSPITAL MATER DEI

Patient Name

ID No. | D.O.B. | Age

Admission Date | Orthopaedic 1st Assessment Date

Ward | Orthopaedic Consultant

Trauma Type

Description

Site

R L

Page 1 of 4

HOSPITAL MATER DEI

Past Medical History

Diabetes Mellitus ☐ Asthma ☐ Thyroid Pathology ☐

Hypertension ☐ Chronic Kidney Disease ☐ Rheumatoid Arthritis ☐

Ischaemic Heart Disease ☐ Epilepsy ☐ Parkinson's Disease ☐

COPD ☐ TIA/CVA ☐ Dementia ☐

Previous Fracture

Other

Past Surgical History

Previous Anaesthesia Y N Not Sure

Anaesthetic Complications

Social History

Smoker Y N ____ cigarettes per day for ____ years from age ____

Alcohol Y N Units/day _____

Home status Alone ☐ With Someone ☐ _____

Mobility Independent ☐ Assisted ☐ Dependent ☐

Mobility Aids ☐ _____

Drug History

Drug Allergies

Pain Management for Trauma Surgery Proforma Page 2 of 4

HOSPITAL MATER DEI

Pain Pre-Operatively – Date: ___/___/___

Pain scale score: ____/10 *for pain scale, please turn over page

Pain description:

Management drug	Dose	Route	Frequency
1.			
2.			
3.			
4.			
5.			

How was pain managed by this Rx?

Operation

Procedure Description | Date

Anaesthesia

General Anaesthesia ☐ Local Anaesthesia ☐

Regional Anaesthesia ☐ No Anaesthesia ☐

Intra-Op Complications

Early Post-Op Complications

Post-Op Plan

Pain Management for Trauma Surgery Proforma Page 3 of 4

MATER DEI

Pain Post-Operatively – Date: __/__/__

Pain scale score: _____/10 **for pain scale, please see below*

Pain description:

Management drug	*Dose*	*Route*	*Frequency*
1.			
2.			
3.			
4.			
5.			

How was pain managed by this Rx?

For scaling pain: *[From Mater Dei's Anaesthesia Dept.]*

1) Obtain a pain score (0-10) "if 0 is no pain at all and 10 is the worst pain you can imagine, what is your pain score right now?"

2) If pain score cannot be obtained, then try with a verbal response scale

"How severe is your pain?"	"Kemm hu qawwi l-uġigħ?"	Score
A) Mild	A) Mhux qawwi	2-3
B) Moderate	B) Moderat	4-5
C) Severe	C) Qawwi	6-7
D) Extreme	D) Qawwi immens	7+

3) Call anaesthetist if in doubt or if not even a verbal response scale can be used

– END –

This proforma is owned by Mr. Kurstein Sant, Dr. Christine Vella and Dr. David Borg, and its purpose is to aid in the orthopaedic audit on 'Pain Management for Trauma Surgery'.

Pain Management for Trauma Surgery Proforma Page 4 of 4

Figure 2. Pain Management Proforma.

RESULTS

The initial recruitment was that of 66. After considering exclusion criteria, 64 patients were considered for evaluation. These patients had been admitted to MDH in view of admittable trauma.

All information was inputted on a spreadsheet for analysis (Figure 3). Some patients were discharged after Day 1 post-operatively. In keeping with this, to decrease bias and help in the data comparison, it was decided that only day 1 post-operatively was to be taken into consideration for all patients. Pain score means were calculated and compared according to the classifications shown in tables 3 and 4. The numbers between tables 3 and 4 differ because 6 fracture patients did not require a procedure.

Classification		Total	Mean Pre-operatively
Total		64	5.73
Trauma type	**Soft tissue**	19	4.68
	Fractures	45	6.18
Gender	**Male**	33	5.45
	Female	31	6.03

Table 3. Mean Pain Score Pre-operatively.

Patient Number	Diagnosis	Pain Scale Score out of 10		Pain Treatment [POST-OP CAHNGES IN RED]					Surgical Procedure Performed
		Pre-Operative	Post-Operative	Paracetamol	Codeine	Diclofenac sodium	Oromorph	Other	
1	Right proximal tibial comminuted fracture w/ displacement	6	4	1g QDS PO	30mg TDS PO		10mg/5ml PRN TDS		ORIF
2	Right intertrochanteric fracture	8	4	1g QDS IV	30mg TDS PO				DHS
3	Right humerus mid-shaft comminuted fracture w/displacement	5	6	1g QDS PO	30mg TDS PO				IM nail
4	LCW left tibia	8	4	1g QDS PO					Washout and closure
5	LCW left foot	2	2	1g QDS PO					Washout and closure
6	LCW left forearm	6	2	1g QDS IV					Washout and closure
7	Right intertrochanteric fracture	9	6	1g QDS PO	30mg TDS PO				DHS
8	LCW right forearm	4	3	1g QDS PO					Washout and closure
9	Right elbow fracture w/ dislocation	5	4	1g QDS PO					ORIF
10	Right leg wound sore after traumatic fall	10	3	1g QDS PO -> IV	30mg TDS PO				Debridement of wound
11	Cellulitis right forearm	0		1g QDS PO					nil
12	Infected sebacecus cyst right forearm	2	0	1g QDS PO					Incision and drainage
13	Cellulitis right lower limb	3		1g QDS PO					nil
14	Left intertrochanteric fracture	8	4	1g QDS PO	30mg TDS PO				PFN
15	Right intertrochanteric fracture	4	2	1g QDS PO	30mg TDS PO				DHS
16	Right trimalleolar fracture	5	2	1g QDS PO	30mg TDS PO				ORIF
17	RA painful episode right knee	8	4	1g QDS PO	30mg TDS PO	50mg TDS PO	10mg PRN/TDS PO		THR
18	Right intertrochanteric fracture	9	4	1g QDS IV	30mg TDS PO		10mg PRN/TDS PO		DHS
19	Pelvic crush injury	8		1g QDS IV					nil
20	Right intertrochanteric fracture	6	4	1g QDS PO	30mg TDS PO				DHS
21	Right patellar fracture	7	1	1g QDS PO	30mg TDS PO	50mg TDS PO			Tension band wiring
22	Left intertrochanteric fracture	8	4	1g QDS PO	30mg TDS PO				DHS
23	Left mid clavicle fracture	5		1g QDS PO	30mg TDS PO				nil
24	Wound dehiscence post quadriceps repair	8	7	1g QDS PO					Revision of sutures
25	Right trimalleolar fracture + patellar dislocation	4	3	1g QDS PO	30mg TDS PO			Entonox PRN PO	ORIF
26	Painful prominent retrograde IM femoral nail	10	4	1g QDS PO		50mg TDS PO	10mg PRN/TDS PO	Morphine PCA pump IV	Re-do nail
27	Left patellar fracture	7	5	1g QDS PO	30mg TDS PO				Tension band wiring
28	Left subcapital fracture	8	5	1g QDS PO	30mg TDS PO				THR

Figure 3. Google spreadsheet used for data collection. Key: Red rows - Fractures; Blue rows: Soft tissue trauma; Orange cells – no procedure done.

Classification		Total	Mean Day 1 Post-operatively
Total		53	3.68
Trauma type	**Soft tissue**	14	2.86
	Fractures	39	3.97
Gender	**Males**	26	2.67
	Females	27	3.45

Table 4. Pain Score Mean Day 1 Post-operatively.

It was recorded that in almost all cases, post-operatively pain was controlled better than that before the procedure.

Fractures

A pre-operative pain score mean of 6.18 signifies that the average patient admitted due to a fracture had a pain level described as 'Severe' (Table 2). Despite this, 31.1% of these patients were not prescribed a second analgesic and left only on paracetamol. Figure 4 illustrates what patients were prescribed as a percentage over total fracture admissions. Codeine with paracetamol represents the most common combination of analgesia.

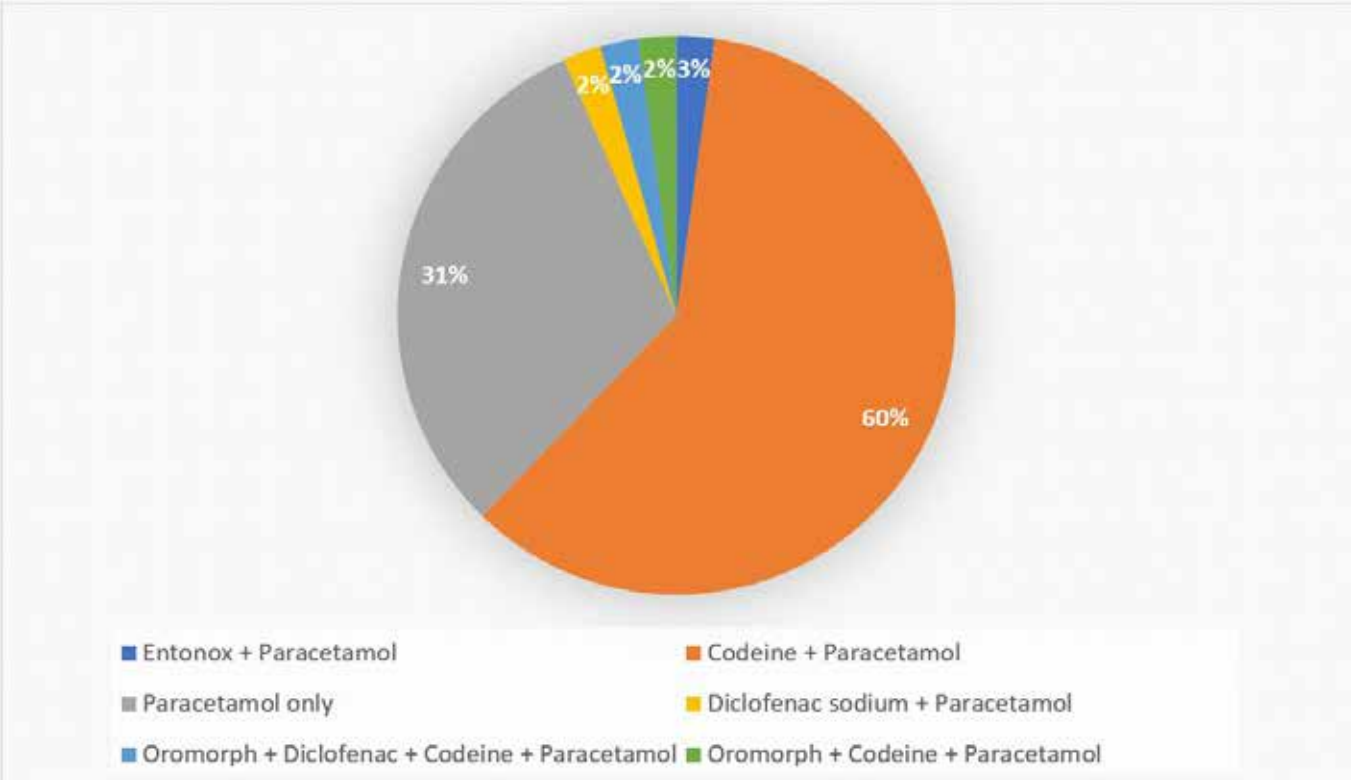


Figure 4. Pie chart demonstrating analgesia prescribed pre-operatively for fractures. [Entonox is a gas mixture composed of 50% nitrous oxide and 50% oxygen].

Soft tissue trauma

A mean of 4.68 signifies that the average soft tissue trauma patient had a pain level described as 'moderate' (Table 2). Paracetamol was the analgesic of choice for soft tissue trauma patients, being prescribed in 68.4% of the total number of patients pre-operatively. 63% of the population was prescribed paracetamol only, whilst 5% were managed with paracetamol and codeine. Despite the fact that only one analgesic was administered in the majority of patients, most of these patients' pain improved post-operatively, where the mean pain score was at 2.86 - described as 'discomforting' or 'mild'. Figure 5 shows a pie chart illustrating what patients were prescribed as a percentage over total soft tissue trauma admissions pre-operatively.

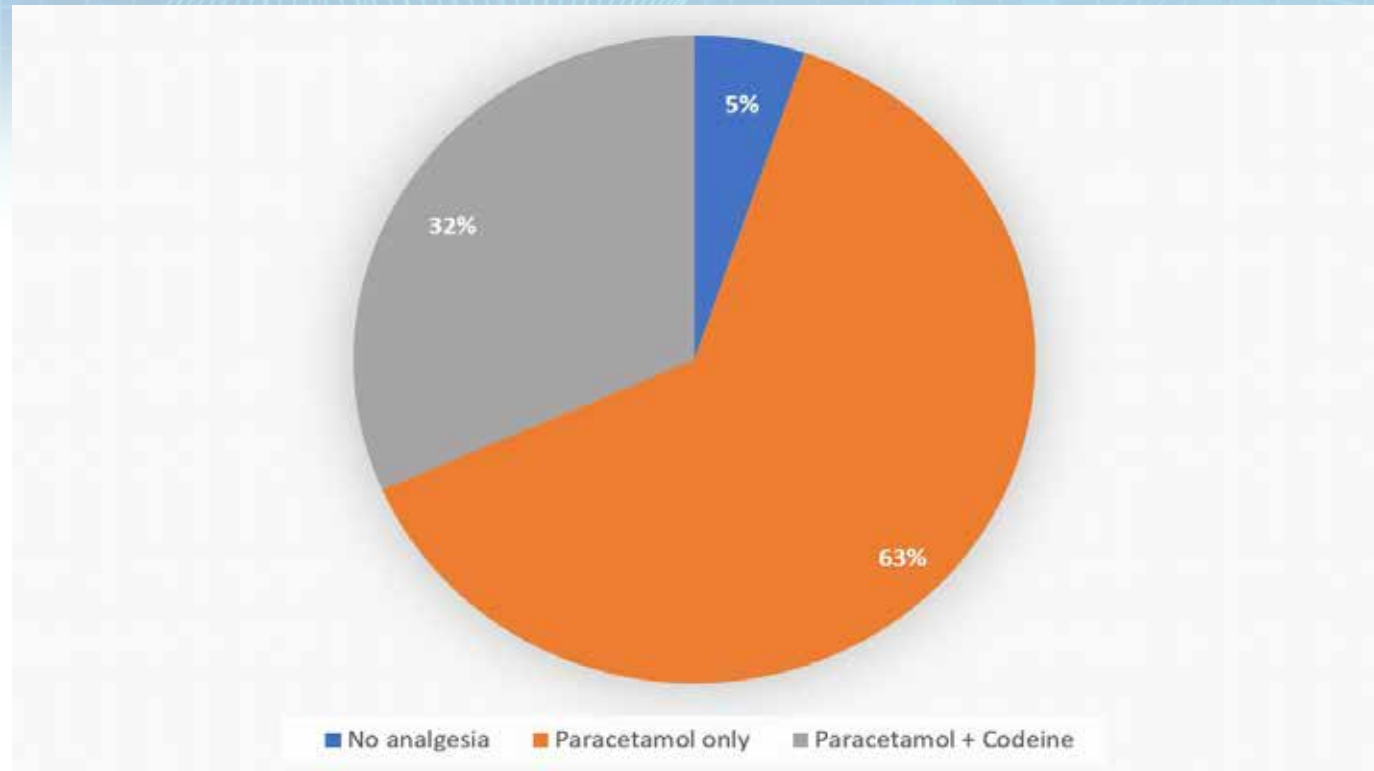


Figure 5. Pie chart demonstrating analgesia prescribed pre-operatively for soft tissue trauma patients.

Gender

In fractures, 20 males and 25 females had mean pain scores of 5.75 and 6.44 respectively. In soft tissue trauma, 13 males and 6 females had a mean pain score of 5 and 4 respectively.

Age

The patients were further categorised into age groups as shown in Figure 6. It was noted that there was no trend in pain score when comparing these age groups. Table 5 represents the number of patients per age group.

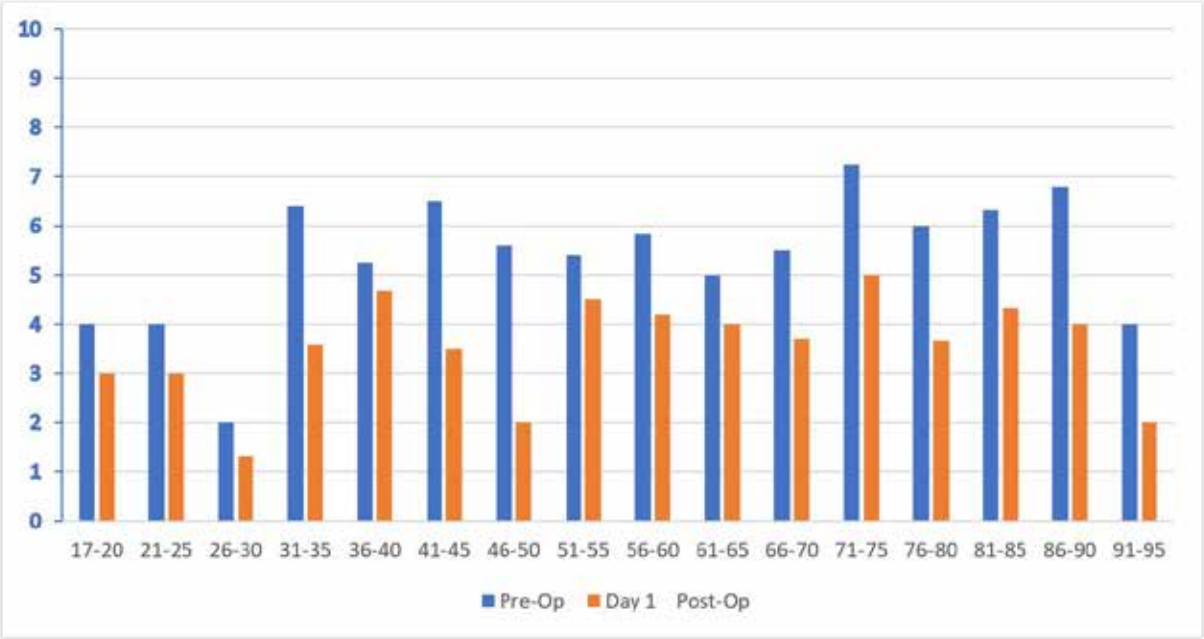


Figure 6. Illustrating pain score on y-axis against ages on x-axis.

Age	Total		Age	Total	
	Pre-Op	Day 1 Post-Op		Pre-Op	Day 1 Post-Op
16-20	1	1	**56-60**	6	5
21-25	1	1	**61-65**	2	2
26-30	3	3	**66-70**	8	7
31-35	5	5	**71-75**	8	6
36-40	4	3	**76-80**	4	3
41-45	2	2	**81-85**	3	3
46-50	5	5	**86-90**	5	4
51-55	5	2	**91-95**	2	1

Table 5. Total population per age category.

LIMITATIONS

- Lack of detailed categorization: The patients were not categorized in detail according to the type of fracture or soft tissue trauma, which limits the ability to compare pain scores between different types of trauma. Moreover, categorization could aid in the comparison of genders and ages and increase accuracy.
- Small cohort size which limits the ability to draw conclusions about the relationship between age and pain scores.
- The audit only considered the use of analgesics and did not evaluate other pain management techniques such as physical therapy or nerve blocks, which also play a role in managing pain in trauma patients.

RECOMMENDATIONS AND WAY FORWARD

Pain is very subjective. It is important to use a stepwise approach when prescribing analgesics depending not only on the patient's pain score but also on the type of trauma the patient experiences. The patient needs to be subsequently monitored for adverse effects to alter treatment if need be as per established guidelines.[2] In keeping with this it is recommended that future studies include a follow-up period after the patients have been discharged from the hospital, which would enable an assessment of the long-term effects of the analgesia, including adverse effects, prescribed for pain control.

RECOMMENDED ANALGESIA FOR ADULT TRAUMA ADMISSIONS

The authors found that analgesia was administered as recommended by the WHO analgesic ladder.[2]

- Mild pain: oral/IV paracetamol
- Moderate pain: Oral/IV paracetamol and codeine
- Severe pain: Oral/IV paracetamol, codeine and PO/IV morphine

Adverse reactions can be mitigated by administering the medications at appropriate time intervals, with food, and if necessary, with appropriate medication example antiemetics, antacids, and laxatives.

Fractures have a higher overall pain score average and therefore should be treated differently compared to soft tissue trauma. For this reason, it is suggested that these patients are immediately started on oral or intravenous paracetamol, with codeine administered every 8 hours as well as oral morphine as needed (PRN), and if not contraindicated. On the other hand, soft tissue trauma admissions should be started on oral/IV paracetamol with codeine prescribed as needed as the first step.

NSAIDS given to supplement pain relief should be used with caution as they have been associated with delayed bone healing. NSAIDS should not be offered to frail or elderly patients as these increase risk of gastrointestinal bleed and renal function impairment.[3]

CONCLUSION

Recognising and assessing pain is crucial for proper pain management. The administration of pain medication should be based on prescribing the most effective drug for the patients which has the least adverse effects when considering the patient's parameters.

In view of the above pain score means, pain management can be improved especially for patients admitted with fractures. Regular assessment of the pain score would help alter a patient's analgesic treatment as needed. Having guidelines which one can follow can help to strategically treat pain according to the patient's needs.

In 2023 posters containing the Pain Management Proforma will be handed out to orthopaedic staff at MDH including doctors and ward nurses, and distributed in all orthopaedic wards. An email containing the poster itself and accompanying instructions will be disseminated to all doctors working at MDH to make sure these changes are implemented. A re-audit will be done five months after this is implemented to ensure the required improvements are making effect.

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PAC3

SILVAN MIFSUD

Family Businesses

Time to Shape up!

We have no official statistics that show how many family businesses operate in Malta. What we know is that according to the latest statistics around 98% of businesses in Malta are Small & Medium Enterprises[1] (i.e. employing 250 persons or less). We also know that the vast majority are family owned and/or family run. Presently we have 259 businesses[2] that are registered with the Family Business Office, meaning that they fall within the definition of what constitutes a Family Business according to the Family Business Act (Chapter 565 of the Laws of Malta)

The definition of what constitutes a family business in the Family Business Act is rather restrictive, as it is defined as a business that is registered as a Limited Liability Company or Partnership where: a) at least two owners are family members within the same family, b) no single family member holds more than 80% shareholding or interest in the structure, c) at least one family member is formally involved in the general governance, proper administration and management of the business structure.

This means that all those family businesses that are run as a sole trader or those family businesses being a company that are officially owned by a single family member, although many other family members are involved in it, are not officially recognised as family businesses by the Family Business Act. This does not mean that in reality they are not family businesses. This may include private medical clinics, dental clinics, as well as pharmacies. We are also increasingly seeing the emergence of small chains of clinics and pharmacies.

"Family businesses ... may include private medical clinics, dental clinics, as well as pharmacies. We are also increasingly seeing the emergence of small chains of clinics and pharmacies"

However, it is officially accepted by all, that family businesses form the backbone of Malta's economy, which is why it is in everyone's interest that we have good performing and solid family businesses.

As an advisor to family businesses for several years, I have experienced first-hand the strengths and weaknesses of family businesses. On one hand, family businesses have the common strength of having a long-term view of things. They normally know that they are in business for the long haul and thus even when they invest, they have a view that the returns from an investment is to be delivered over a long-term period. On the other hand, family businesses have a number of weaknesses that they would do best to work upon to mitigate them, especially as we are now likely going to enter a period with less economic buoyancy. What are these weaknesses?

- They lack a strategic mindset. Many family businesses are completely engulfed by an **Operation mindset** – the mindset that focuses on daily issues and with a clear focus on just internal matters. As we are now in a period of very fast change, family businesses need more a **Strategic mindset**, with a clear focus on what happens around them, how the market landscape and consumer preferences are changing and hence how best to respond to these changes. Unfortunately, many family businesses get lost in firefighting the present, rather than planning the future.

- As an indirect result of the lack of a strategic mindset, they lack appropriate corporate and family governance structures. The first thing I ask when I visit for the first time a family business is not to review their financial statements, but a more simple question, "Where do you meet to discuss things over?". You would be surprised to learn that many family businesses either do not have such a space where the family business leadership can meet to discuss and decide or otherwise the space they have is inadequate as it is either too small or lacks basic facilities. Family businesses badly need corporate governance structures like an effective and functioning board of directors, preferably with some independent,

non-executive director on the board. They also need other governance structures like a family forum to balance the rights and duties of family members who are involved in the business and those that are not.

- Lack of succession planning. As I keep repeating, succession planning is a journey and not an event. However, a common mistake I see in family businesses is that they keep postponing finding time and work on succession planning. This results that they are being caught out – many times trying to do something about it when it's too late. Succession planning is a journey and requires careful planning and effort from all angles, both from the older generation and the new generation. It requires that on one hand the older generation is able to pass on the baton, whilst training and then letting go, while on the other hand the new generation proves its skills and commitment, whilst still being allowed space to come forth with its own ideas.
- Lack of policies. Many family businesses lack formal policies with regards dividend distribution, family employment and how to preserve the family wealth. These policies become very important beyond the first generation as more family members are likely to be involved in the business in one way or another.

The final takeaway message is simple. I hope all family business owners realise, that since change around them is happening at an increasing accelerated pace, they cannot keep operating like many of them did in the past. As I keep repeating, what made family businesses successful in the past will not be what will make them successful now and in the future. Maintaining an amateurish and informal approach to the way a family business is run is directly equitable to burying one's head in sand.

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MS CHRISTINE PORTELLI

Minimal Access Surgery in Gynaecology

INTRODUCTION

Significant technological advances have widened the use of laparoscopy in gynaecology, as well as in other surgical specialities such as urology, gastroenterology, and general surgery. Laparoscopy is a minimally invasive surgical technique used for both diagnostic and therapeutic purposes. Laparoscopy offers several benefits over traditional open surgery. Typically, the incisions are small and only a few millimetres in length. This minimally invasive approach results in less damage in the surrounding tissue, hence less pain with shorter hospital stays and recovery times when compared to open surgery.[1-4] Most patients are able to resume their normal activities within 2-3 weeks. Minimally invasive surgery has been shown to be associated with reduced risks of complications when compared to open surgery in particular lower risks of bleeding,[5] infections, adhesions[6] and damage to any of the surrounding organs.

Laparoscopy also provides better visualisation of the internal organs which allows for more accurate diagnosis and treatment. This has been improved through advances in technology including the use of high definition cameras.

Some common gynaecological procedures that can be performed using laparoscopy include:

- Diagnosis and treatment of endometriosis
- Removal of ovarian cysts or tumours and risk-reducing surgeries
- Management and treatment of ectopic pregnancy
- Tubal sterilisation
- Myomectomy
- Hysterectomy
- Treatment of pelvic adhesions.

INDICATIONS OF LAPAROSCOPY

Diagnostic Laparoscopy

This is the most common laparoscopic procedure performed in gynaecology and is used to diagnose a variety of gynaecological conditions, including endometriosis, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and malignancy.[7]

Laparoscopy has become the mainstay in the assessment and management of fertility.

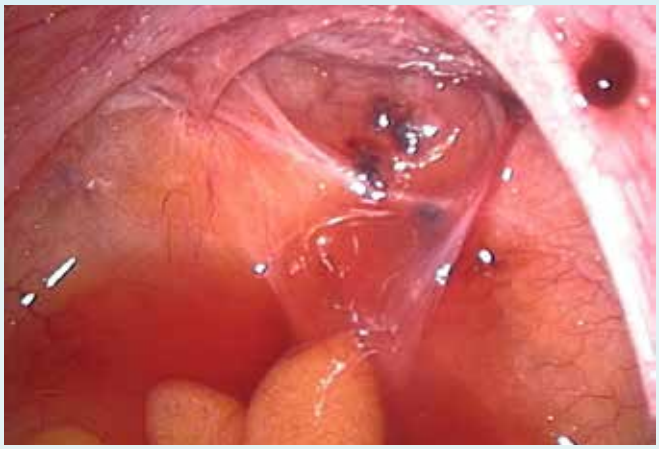

Figure 1. Endometriosis in the Pouch of Douglas.

Treatment of Endometriosis

Laparoscopy is the most common procedure used to diagnose and treat endometriosis[8] and is considered the gold standard to diagnosis this condition. Delays of up to 10 years can occur between the first reported symptoms and confirmation of the diagnosis. Many women report that the delay in diagnosis leads to increased personal suffering, prolonged ill-health and a disease state that is more difficult to treat. The diagnosis of endometriosis can be challenging as patients present with a wide and varied spectrum of symptoms. Endometriosis lesions may be resected or ablated during laparoscopy. Both of these techniques have shown to improve fertility and decrease pelvic pain in multiple well-designed studies. A systematic review by Franck et al. reported improvements in the quality of sexual life following laparoscopic surgery for endometriosis.[9]

Adnexal Surgery

Ovarian Cystectomy

Up to 10% of women will have some form of surgery during their lifetime due to the presence of an ovarian mass.

The overall incidence of a symptomatic ovarian cyst in a premenopausal female which is malignant is approximately 1:1000 increasing to 3:1000 at the age of 50.

A laparoscopic approach is generally considered to be the gold standard for the management of benign ovarian masses.[10-14] Benign ovarian cysts ≥ 6cm that persist over two

or more cycles in a premenopausal, nonpregnant female are not likely to resolve and a cystectomy is indicated. This can be achieved using laparoscopy as this has been shown to reduce morbidity with a shorter recovery time and earlier hospital discharge. The early return to work and resumption of normal activities has important socio-economic benefits.[15]

Salpingo-oophorectomy

The incidence of cysts in postmenopausal women is 5-17%[16,17] and with the increasing use of various imaging modalities a large proportion of these cysts are often an incidental finding. In turn, the vast majority of these cysts are benign. It is important to appropriately manage these, and most importantly distinguish these from the potential malignant ones. Salpingo-oophorectomy may be more appropriate in postmenopausal women with a growing or persistent ovarian cyst. Laparoscopy has been shown to reduce morbidity and improve outcomes in the appropriately selected cases and when performed by suitably trained surgeons. Patients should be counselled that staging laparoscopy or laparotomy may be required if malignancy is revealed at the time of the laparoscopy.

Women with a genetic predisposition of developing gynaecological cancers such as those with BRCA1, BRCA2 or Lynch syndrome have a substantially reduced risk of developing cancer following a laparoscopic bilateral salpingo-oopherectomy when performed as a risk-reducing surgery.

Treatment of Ectopic Pregnancy

Laparoscopy is the surgical approach of choice for most ectopic pregnancies. A salpingostomy or salpingectomy may be performed to remove the embryo and/or gestational sac. The advantage of operative laparoscopy for ectopic pregnancy over laparotomy is well recognised. It is associated with shorter operation times, less intraoperative blood loss, shorter hospital stay, lower analgesic requirements, and in keeping with this, significantly lower costs.[18-20] Also, patients are significantly less likely to develop adhesions after laparoscopic surgery.[21]

Tubal Ligation

Tubal sterilisation can be done in various manners, i.e. by using electrosurgery to desiccate the tubes, the application of clips or silastic bands, or complete removal of the fallopian tubes. The latter is also known as opportunistic salpingectomy and is increasingly recommended in women undergoing other pelvic surgery such as hysterectomy. The most common type of epithelial ovarian cancer (90% of ovarian cancers), called high-grade serous ovarian cancer (HGSC), is found to originate in the fallopian tubes before spreading to the ovary.[22] Tubal sterilisation can also be carried out to occlude the tubes at the mid-isthmic portion as a permanent form of contraception.

Myomectomy

Uterine fibroids (also called leiomyoma or myoma) are the most common benign tumour among women of childbearing age. Although uterine fibroids are common, they can be asymptomatic in most of the women. Symptomatic patients can have a wide range of symptoms:

- Dysfunctional uterine bleeding
- Mild to severe anaemia
- Pressure effects in pelvic area
- Pelvic pain
- Infertility
- Recurrent miscarriages.[23]

New surgical techniques relating to minimal invasive surgery such as laparoscopic myomectomy and many others have been developed as an alternative to open myomectomy.[24] Some women with a symptomatic fibroid uterus prefer to preserve fertility. The fibroid may be removed by morcellation or colpotomy. In a Cochrane review, laparoscopic myomectomy was associated with less postoperative pain, reduced febrile morbidity and shorter hospital stay than in the open myomectomy cohorts.[25] Although open hysterectomy is technically easier than a laparoscopic hysterectomy, laparoscopic myomectomy leads to faster and smoother recovery periods.[26] In 2020 the Food and Drug Administration (FDA) issued recommendations that power morcellation should only be used with a compatible tissue containment system.[27]

Hysterectomy

Hysterectomy is used to treat many health conditions. Some of these conditions include:

- Uterine fibroids (this is the most common reason for hysterectomy)
- Endometriosis
- Pelvic support problems (such as uterine prolapse)
- Abnormal uterine bleeding
- Chronic pelvic pain
- Gynaecologic cancer or reducing cancer risk.

The three basic laparoscopic approaches for hysterectomy are laparoscopic-assisted vaginal hysterectomy (LAVH), laparoscopic hysterectomy (LH), and laparoscopic supracervical hysterectomy (LSH). The difference lies in the approach used to divide the uterine vessels. In LH and LSH, the uterine vessels are divided laparoscopically. In LSH, the cervix is not removed. In a LAVH, the uterine vessels are divided from the vaginal approach.

LSH is most often promoted for benign indications in particular as the operating time and recovery period are decreased and the risk of both infection and ureteral injury are minimised. However, an increased risk exists for

reoperation for cervical bleeding and prolapse. Furthermore, patients must follow the recommendations for regular cervical cytology.

Adhesions

Adhesions may form due to prior infection, such as a ruptured appendix or pelvic inflammatory disease (PID), endometriosis, or previous surgery. Adhesions may contribute to infertility, bowel obstruction, chronic pelvic pain and difficulty in any future abdominopelvic surgery. They can also make it more difficult to visualise the internal organs during diagnostic and therapeutic surgical procedures. The risk of adhesions after laparoscopy can vary, depending on several factors, including the extent of the surgery and the individual patient's health status. Studies have estimated that between 67-93% of patients who have undergone open abdominal surgery may develop adhesions.[28] Studies have shown that the risk of adhesions forming is lower than after open surgery. [29]

CONCLUSIONS

In recent years, three innovations that have been introduced to the field of laparoscopy i.e. single incision laparoscopy (SILS), robotic surgery[30] and natural orifice transluminal surgery.[31] All three have their advantages and disadvantages compared to traditional laparoscopy. Of these three developing technologies, robotic surgery is having the largest impact on clinical care in particular in gynae-oncology. The robotic system allows surgeons to perform procedures that previously would have been performed via laparotomy, using modified laparoscopic procedures.

Complications may occur for various reasons. The use of trocars, and their placement on the abdominal wall and pneumoperitoneum in laparoscopy pose unique risks to this surgical approach. The increased intra-abdominal pressures associated with laparoscopy increases anaesthesia-related risks such as aspiration and increased difficulty in ventilation. Furthermore, the delivery of energy within the abdominal cavity during electrosurgery likewise introduces risk. Although the risk of blood loss is relatively low for most procedures, potentially massive blood loss may also occur.

Laparoscopy shares characteristics of both minor and major surgery. To patients, laparoscopic procedures often seem to be minor surgical interventions because of the small incisions, relatively small amount of postoperative pain, and short convalescent period.

Overall, laparoscopy is a safe and effective surgical technique that offers numerous benefits over traditional open surgery. It has become a common procedure in gynaecology due to its many advantages of shorter recovery period, earlier return to work, reduced hospital stay and reduced risk of adhesions and better aesthetic incisions, whilst improving diagnoses to correctly treat women from various gynaecological conditions.

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DR PIERRE VASSALLO

Ultrasound Imaging of Groin Hernias

Abdominal wall hernias occur where structures that are normally located within the peritoneal cavity protrude through a defect in the abdominal wall muscles.

The worldwide lifetime incidence of abdominal wall hernias is approximately 5%, with 80% of hernias occurring in the inguinal canal and 5% in the femoral canal. The remaining 15% include incisional, spigelian, umbilical, epigastric and other hernia types.[1]

Groin hernias are classified into two groups: those originating along the inguinal canal and those originating outside the inguinal canal. The former group include direct and indirect inguinal hernias and the latter, femoral and spigelian hernias.

INGUINAL HERNIAS

Inguinal hernias occur when the processus vaginalis, an embryological channel, fails to obliterate. The testicle is an intraperitoneal organ that develops during the embryological period from the urogenital ridge that lies adjacent to the lumbar spine.[2] The processus vaginalis opens to allow descent of the testicle from its paraspinal site of origin into the scrotal sac; this descent is completed by around the 36th week of pregnancy (Fig 1). In females, the inguinal canal contains the round ligament of the uterus.

The inguinal canal normally obliterates after passage of the testicle or round ligament. However, it may remain partially or completely open. If incompletely closed, it constitutes a point of weakness that may allow herniation of intra-abdominal contents. The canal courses from lateral to medial through the muscle layers of the abdominal wall from the deep inguinal ring to the superficial inguinal ring (Fig 2). A hernia occurring along the course of the inguinal canal is called an indirect hernia. A direct hernia occurs when weak abdominal wall muscles and tendons bulge directly through the external inguinal ring.

Ultrasound imaging (US) is useful for confirming the presence of a hernia and identifying its type and content. The normal inguinal canal is readily visualised with the US probe positioned just above and parallel to the inguinal ligament (Fig 3).

US is useful in confirming the course of an indirect inguinal hernia that starts at the internal inguinal ring lateral to the inferior epigastric vessels and courses medially anterior to the vessels to the external inguinal ring (Fig 4).

A direct hernia does not follow the inguinal canal; it bulges through the weak lower abdominal wall muscles directly into the external inguinal ring. It therefore lies medial to the inferior epigastric artery (Fig 5). Dynamic imaging during Valsalva manoeuvre or in the standing position is useful since the increased intra-abdominal pressure improves visibility of the hernia and gives a better assessment of its size.

The content of a hernial sac should be clearly identified, which most commonly consists of omentum. However, a hernial sac may contain bowel and occasionally an ovary or uterine fibroid. In females, a persistent processus vaginalis is often referred to as the canal of Nuck. A large canal of Nuck, particularly in female infants, may contain an ovary and/or part or all of the uterus (Fig 6). Complications such as incarceration and strangulation are more likely to occur with non-omental content.

Incarceration is identified on US by the fact that the hernia cannot be reduced by compression with the US probe. Incarceration increases the risk for strangulation, which occurs when the blood supply of the hernial contents is compromised. This may lead to ischaemia and gangrene of the hernial contents. Strangulation is more likely to occur when a narrow neck of the hernial sac is present. US features of strangulation include fluid collections in the sac, bowel wall thickening and diminished perfusion of the contents on colour Doppler imaging (Fig 7).

FEMORAL HERNIAS

Femoral hernias occur in the femoral canal. The canal is located medial to the common femoral vessels within the femoral sheath. The femoral sheath originates as a fibrous extension from the inferior aspect of the inguinal ligament (Fig 8).

On US, femoral hernias lie below the inguinal ligament and medial to the common femoral vein

and may contain omentum, small bowel, and other intraperitoneal structures (Fig 9). Femoral hernias show a predilection for the right side and are more common in females.[3]

SPIGELIAN HERNIAS

A Spigelian hernia is not a true groin hernia as it occurs well above the groin through a congenital or acquired defect in the Spigelian fascia. The Spigelian fascia is located between the lateral border of the rectus abdominis muscle and the medial borders of the transversus abdominis, internal and external oblique muscles (Fig 10). A spigelian hernia is relatively rare, usually developing after age 50, primarily in men. The cause is usually a weakening of the abdominal wall, trauma, or prolonged physical stress. Spigelian hernias are sometimes challenging to diagnose.[4]

RISK FACTORS FOR COMPLICATIONS AND SELECTING TREATMENT OPTIONS

The risk factors useful in predicting complications in an adult patient with groin hernia are age (older age group), duration of hernia (recent sudden onset), type of hernia (femoral more than inguinal) and coexisting medical illness. In children, the risk factors are age (very young), gender (male), recent sudden onset of hernia and side (right side).[5]

Groin hernias particularly those predisposed to or showing signs of complications should be managed promptly surgically. The aim is to reduce the hernia contents if they are healthy and to close the hernial orifice. Resection of ischaemic contents would be required in case of infarction or gangrene. Elective surgery may be performed laparoscopically, which decreases post operative pain and recovery time but requires general anaesthesia. Open surgery may be done under local anaesthesia, which is safer for high-risk elderly individuals.

CONCLUSION

The inferior epigastric artery at its origin is a critical anatomic landmark in differentiating indirect from direct inguinal hernias. Femoral hernias occur medially to the femoral vein and inferiorly in relation to the inguinal ligament. Spigelian hernias occur at the lateral margin of the rectus abdominis through the Spigelian fascia. Understanding the regional anatomy and the types of hernias that occur in this location assists sonographic diagnosis and helps planning appropriate surgical treatment.

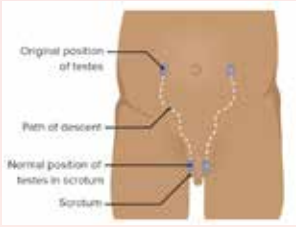


Figure 1: Diagram showing the site of origin of the testis and its path of descent into the scrotum. Ref. https://www.lecturio.com/concepts/cryptorchidism/

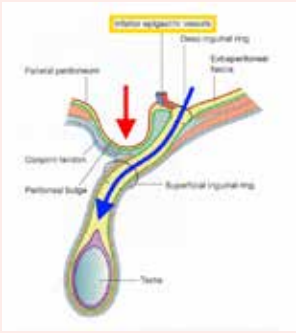


Figure 2: Diagram[6] showing the inguinal canal in yellow coursing through the abdominal wall muscles. The blue arrow indicates the path of an indirect inguinal hernia, while the red arrow shows that of a direct hernia. The inferior epigastric vessels are used as a landmark to distinguish indirect hernias from direct hernias, with the former originating laterally while the latter originates medially.

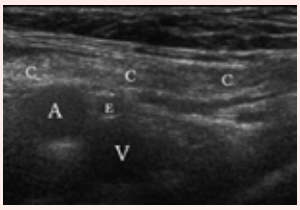


Figure 3: US image oriented parallel to and just above the inguinal ligament showing the normal inguinal canal (C) containing the spermatic cord. The canal starts lateral to the inferior epigastric artery (E) and courses anterior and medial to it. A – external iliac artery, V- external iliac vein.[3]

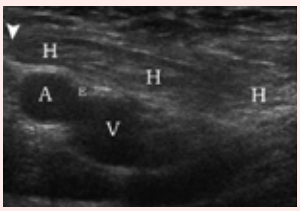
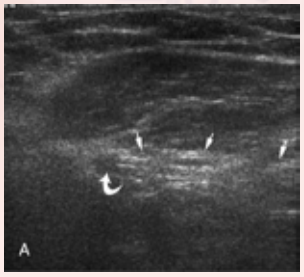


Figure 4: US image oriented parallel to and just above the inguinal ligament shows an omentum-containing indirect inguinal hernia (H) starting laterally at the internal inguinal ring (arrowhead) and coursing medially anterior to the inferior epigastric artery (E). A – external iliac artery, V- external iliac vein.[3]

Figure 5: US Images[1] of an indirect inguinal hernia.

A. Non-Valsalva image showing the inferior epigastric artery (curved arrow) and the inguinal canal (straight arrows).



B. Valsalva image showing protrusion of a direct inguinal hernia containing omentum (straight arrows) medial to the inferior epigastric artery (curved arrow).

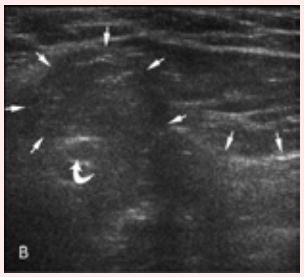


Figure 6: US image of the right groin in an infant shows herniation of an ovary (black arrows) and uterus (white arrows) into the canal of Nuck.[7]

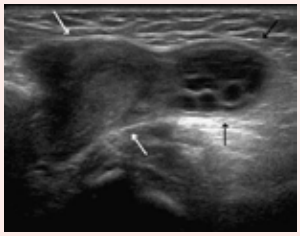


Figure 7: US image of an indirect inguinal hernia that extends into the scrotum. Note thickened walls of small intestinal loops (arrows) and the presence of fluid (F) in the hernial sac. Case courtesy of Townsville radiology training, Radiopaedia.org, rID: 17968.

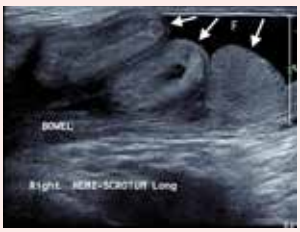


Figure 8: Femoral Canal Anatomy: The femoral canal (purple) is located in the femoral sheath medial to the common femoral vein (dark blue). https://teachmeanatomy.info/lower-limb/areas/femoral-canal/

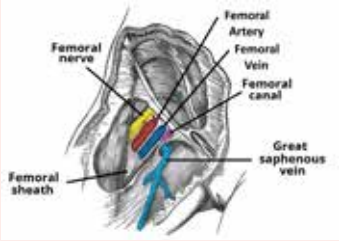


Figure 9: US image of a femoral hernia showing a hernial sac containing omentum (open arrow) lying medial to the femoral vein and artery (FV, FA). Case courtesy of Maulik S Patel, Radiopaedia.org, rID: 25936.

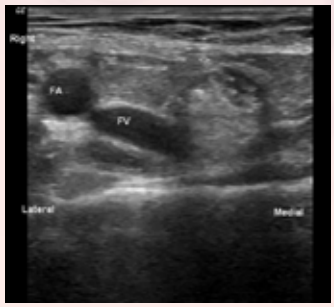


Figure 10: Anatomical diagram showing the location of the Spigelian fascia between the rectus abdominis muscle medially and the transversus abdominis, external and internal oblique muscles laterally. https://www.researchgate.net/figure/Anatomical-diagram-showing-the-relationship-between-the-rectus-abdominis-muscle-RA_fig2_312473946

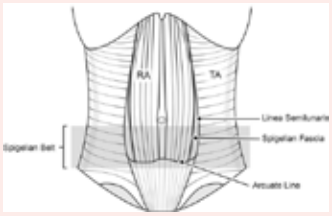
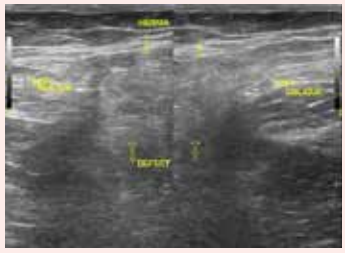


Figure 11: US image of a Spigelian hernia, note that extraperitoneal fat is herniating between the left rectus abdominis muscle medially and the left oblique muscles laterally. Case courtesy of Maulik S Patel, Radiopaedia.org, rID: 29329.



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DR ALFRED GRECH, DR MARIO FARRUGIA, DR MICHAEL BALZAN

Drug Repurposing

ABSTRACT

The discovery and development of new drugs is slow, time-consuming and costly. An increasingly attractive option is 'repurposing', which is the process of finding new uses for existing drugs. This proposition of repurposing (also called 'drug repositioning') has spurred the research community as it has a promising potential to fast track already used drugs into clinical studies for new clinical indications.

INTRODUCTION

There are several advantages of repurposing drugs. Perhaps the most important one is that there is a lower failure risk. This is because the repurposed drug has already been found to be safe in clinical trials. Another advantage is that there is less investment to repurpose a drug. In fact, it has been estimated that on average 275 million euros are needed to repurpose, while for a new drug discovery it ranges between 2 to 3 billion euros. The repurposing strategy also has a reduced time frame when compared to the conventional drug discovery. Indeed, generally, a conventional drug discovery takes from 10 to 17 years. On the other hand, it takes from 3 to 12 years for a drug to be repurposed. The shorter time frame becomes more practical in pandemics. For example, in the ongoing Covid-19 pandemic, there have been about 25 repurposing trials in clinicaltrial.gov.

DRUG REPURPOSING STRATEGIES

The task of repurposing navigates around the relationship between drugs, targets and diseases. Traditionally, drug targets were selected from approximately 20,000 genes in the human genome. So only about 1-2% of the human genome was currently a potential drug target. This is surely to increase in the near future, given the fact that the non-coding regions of the genome are also being deciphered and targeted. When it comes to the disease aspect, one finds difficulty to give an estimate because diseases are really a spectrum, and one cannot draw boundaries. But one can say that there are about 14,400 diseases in total, of which about 7,000 are rare diseases. The rare diseases were traditionally neglected by pharmaceutical companies but this trend is also changing.

Drug repurposing can be approached through three main methods, specifically 'target-centric', 'drug-centric', and 'disease-centric' repositioning. The target-centric strategy tries to find a new indication for a target that is already deciphered. In drug-centric repurposing, the aim is to find a new target for a known drug. In the disease-centric repurposing, focus is on the pathophysiological pathways of diseases, whereby any revealed similarity is investigated and exploited. Through a retrospective analysis, Parisi et al.[1] found that several cases of repurposing were based on drug-target interaction approaches.

This essay will not be dealing with serendipitous discoveries, even though such discoveries can be a source of untapped opportunity. Suffice to say that serendipity here means the accidental discovery of a new clinical drug indication. Examples include Viagra® (researchers were conducting research o n drug moieties for antihypertensive properties and during the process they found that sildenafil could be used for erectile dysfunction) and Regaine® (initially minoxidil was used as an antihypertensive but later found a niche market for hair growth).

A. DRUG-CENTRIC APPROACHES

Table 1 lists some of the drug-centric approaches. Often these approaches are coupled together.

Technologies
1. Computational Ligand-based approach
2. Computational Structure-based approach
3. Protein expression profiling (Chemical Proteomics)
4. Off-target screening

1. *Computational ligand-based approaches* are virtual screening approaches. They aim to reveal pharmacophores, which are functional groups within a prospective compound that are responsible for a biological response.[2] Generally, pharmacophore mapping is used when no information about the target structure is available.

Daoud et al.[3] used this approach, with other tools, to create a pharmacophore model to repurpose antiviral drugs against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which is responsible for the current Coronavirus Disease 2019 (COVID-19) pandemic. Specifically, they found five antiviral drugs which successfully docked into the binding site of COVID-19 main protease (lopinavir, remdesivir, ritonavir, saquinavir and raltegravir) which are already approved by the FDA.

Pérez-Sánchez et al.[4] used pharmacophore mapping and 3D shape similarity (see paragraph below) on a comprehensive drug database called Drugbank and identified 108 hits from 11,353 compounds. From these hits

they found eight molecules that were structurally similar to pyridostigmine. The latter is an acetylcholinesterase inhibitor (AChEI) which is used in the management of Alzheimer's disease.

2. *Computational structure-based approach* is also a virtual screening approach. It uses the 3D structure of the biological target to identify how an active drug binds to the 'active site' of the target. Knowledge of this 'molecular docking' between the target and drug is then used to discover other drugs.[5] Such a virtual molecular docking method is also used in 'target fishing' or 'inverse docking', where drugs are investigated to bind to other diverse types of targets from databases of known clinical targets.[6]

Choudary et al.[7] used the structure-based virtual screening approach and investigated a library of drugs called LOPAC. Their aim was to find prospective drugs against the ACE2 receptor of human cells and against the receptor binding domain of spike protein (S-RBD) of SARS-CoV-2. They found some promising molecules and propose that these can be used against SARS-CoV-2.

Wang et al.[8] also used a structure-based virtual screening to interrogate an FDA approved drug database for prospective Cytochrome P450 1B1 (CYP1B1) inhibitors. Cytochrome P450 1B1 is a target in cancer prevention and therapy. They identified six compounds, amongst which were carvedilol and indacaterol.

3. *Chemical Proteomics* is a main branch of proteomics. Its aim in repurposing is to identify the numerous protein targets of active small molecules.[9,10] Le et al.[11] screened commercially available kinase inhibitors for any antibacterial properties that could kill methicillin-resistant *Staphylococcus aureus* (MRSA). They found sorafenib, an anticancer drug, to be a potential candidate. Chemical proteomics, in their investigation, also revealed the probable mode of action of sorafenib that was responsible for the killing of MRSA.

Chemical proteomics were pivotal in the study of Lum et al.[12] Specifically, they investigated the global cellular interactions between lipids and proteins and the effects of active small molecules that included natural products but also repurposed drugs. They showed that the antifungal miconazole inhibits sphingosine-1-phosphate (S1P) lyase. This inhibition decreases the severity of multiple sclerosis in experimental models.

4. *Off-target-screening* is based on the fact that drugs cause side-effects because they bind with other targets that are somewhat similar to the original target. Thus, the study of these other homologous targets in other diseases offers another platform for drug repurposing.

Sprinolactone is an antagonist of the mineralocorticoid receptor and as such is used in the treatment of heart failure, hypertension and cirrhosis. However, it also is an antagonist of the androgen receptor and has been repurposed for the treatment of acne, polycystic ovary syndrome and hirsutism in women.

Another example is the repurposing of doxepin. Doxepin is an antidepressant of the tricyclic class. However, its off-target effects, mediated by histamine H1 and muscarinic receptors, are responsible for its repurposing in pruritus, chronic urticaria and psychodermatology.

Dapsone and thalidomide are another two drugs that were repurposed based on their off-target screening. Dapsone, which is used in leprosy, has been repurposed for its anti-inflammatory effects in several skin conditions like pemphigoid, IgA pemphigus, prurigo pigmentosa and neutrophilic dermatosis, amongst others.[13] Thalidomide, on the other hand was used for morning sickness in pregnancy, but was withdrawn because of its teratogenic effect. Specifically it caused phocomelia (a congenital deformity where the limbs are underdeveloped or absent). This off-target effect was methodically studied and it was found that thalidomide inhibits vascular endothelial growth factor (VEGF) and tumour necrosis factor alpha (TNF-α). Because of its inhibition of VEGF it was repurposed for the treatment of multiple myeloma. Because of its inhibition on TNF-α, it was repurposed to manage erythema nodosumleprosum.[14,15]

B. DISEASE-CENTRIC APPROACHES

Here the homology of the pathophysiological pathways of diseases is the basis of repurposing. Table 2 lists some of the main methods used in disease-centric repositioning.

Technologies
1. Gene expression profiling
2. Phenotypic screening
3. Data Mining (Neural networks, Graph Theory Algorithms)

1. *Gene Expression Profiling*

Bioinformatics and gene expression profiling-has led to the ability to link genetic profiles and drug response. This approach is also being used to systematically repurpose drugs by expanding their spectrum for treatment.

For example, Lee et al.[16] built a strong bioinformatics platform called DeSigN, which can be used for repurposing drugs. By using gene expression profiling, it predicts the candidate drug/s against the cancer cell lines of interest. Another platform called DeepCodex was designed by Donner et al.[17] It links functional similarity of compounds based on data of gene expression.

Another resource for drug repurposing that uses gene expression changes or signatures is the Connectivity Map (CMap). Donertas et al.[18] used it to repurpose drugs to counteract aging in the human brain. They found 24 drugs and propose that some of these drugs can be used as anti-aging drugs.

Qu et al.[19] also used gene expression profiling to find repurposed drugs for the treatment of psoriasis. Their analysis revealed several candidates, amongst which were monobenzone, tiabendazole, resveratrol, doxycycline, parthenolide, and methotrexate.

2. *Phenotypic screening*

This is a method to identify molecules that can alter the phenotype of a cell. Two main methods are used, 'in vivo assays' and 'cell-based (in vitro) assays'. In the in vivo method, screening of compounds is done on preclinical disease models. In the second method, as the name implies, screening of compounds is done on cultivated cells 'in vitro'; the cell culture systems are validated disease models. This phenotypic screening approach is seeing a revival and is being used to overcome the bottleneck of cancer therapeutics, but not only.[20,21]

Using this method, Iljin et al.[22] found that disulfiram can act as an anti-neoplastic drug in prostate cancer. However, a clinical trial (Identifier: NCT02963051) found that disulfiram is ineffective in metastatic, castration resistant prostate cancer because it is metabolically changed into an inactive metabolite. Nevertheless, the authors propose further research to find a stable formulation of disulfiram. Corsello et al.[23] also used this approach using the method 'PRISM' (profiling relative inhibition simultaneously in mixtures) and found 49 non-oncology drugs to have high anti-neoplastic activity.

Phenotypic screening on whole organisms, besides identifying potential cancer drugs, can also reveal their pharmacokinetics and organ-toxicity. Using a transgenic model of zebra fish, Ridges et al.[24] screened the effectiveness of 26,000 small molecules against leukaemia. They fished a molecule called lenaldekar that had potential against various blood malignancies. Although lenaldekar is currently not being investigated in clinical trials, its discovery triggered further research on quinoline derivatives, as prospective candidates to treat leukaemia.[25]

3. *Data Mining – Graph Theory Algorithms; Neural Networks*

Data mining also has great potential in drug discovery and drug repurposing. In recent years, research into cellular functions and processes has generated great knowledge. But this great knowledge has generated difficulties in how to integrate the data into a rational meaningful way. This led to an increase of computational techniques to process, analyse and store the data.

One such tool is that of graph theory, where biological structures and relationships are represented graphically. Gramatica et al.[26] used this mathematical technique to enable drug repurposing by discovering connectivity between drugs and disease.

Another pipeline is that based on 'artificial neural networks', simply called 'neural networks'. Again, these are a series of algorithms that try to decipher relationships in a set of data. These computing systems mimic processes of how biological neural networks work. When such artificial neural networks are made in several layers, the platform is called a 'deep learning' approach. These neural networks offer another strong approach for developing 'in silico' drug repositioning.

Zhou et al.[27] used such a network to rapidly identify potential repurposable drugs against SARS-CoV-2. They identified melatonin, mercaptopurine, and sirolimus as repurposable drugs. Melatonin (N-acetyl-5-methoxytryptamine) is in clinical trials (ClinicalTrials.gov Identifier: NCT04474483, NCT04470297) for its anti-oxidative and anti-inflammatory roles, offering possible protection against organ injuries.

Similarly, Hsieh et al.[28] used a neural network approach together with other tools to repurpose drugs for Covid-19. They fished 22 potential candidate drugs amongst which are Atorvastatin, Azithromycin, Aspirin, Acetaminophen, and Albuterol. Atorvastatin is in clinical trials (ClinicalTrials.gov Identifier: NCT04952350, NCT04380402). As is Azithromycin (ClinicalTrials.gov Identifier: NCT04381962).

Wei Zhang et al.[29] used both network-based and graph theory based algorithms in oncology, to reposition drugs and offer personalized treatment. Sidders et al.[30] coupled a network approach with a phenotypic screening approach to study and identify small molecules that could be potential drug candidates in complex chronic pain diseases.

C. TARGET-CENTRIC

In target-centered drug discovery, researchers use analytical tools (already mentioned) to detail and define a molecular target like a gene or its product or a molecular mechanism. Knowing the molecular target, they then try to find a drug to hit it. In theory, this allows more specificity and less side-effects.

A good example of this approach is the use of antisense oligonucleotides targeting a specific nucleotide sequence in messenger RNA (mRNA). Once there is binding, the mRNA cannot be translated into the protein. Fomivirsen provided the first proof-of-concept for the use of such

antisense oligonucleotides. Fomivirsen was approved by FDA (Food and Drug Administration) in 1998 (and later also approved by EMA (European Medicines Agency)) for treating cytomegalovirus (CMV) retinitis. Other antisense-based drugs were approved like mipomersen which is an antisense oligonucleotide that inhibits apolipoprotien B. It was FDA approved in 2013 for treating homozygous familial hypercholesterolemia. Other examples beside antisense oligonucleotides, are those previously discussed by Grech et al.[31] and include locked nucleic acid anti-miRs, miRNA sponges, miRNA mimics, siRNAs and ribozymes.

CONCLUSION

Recycling old drugs is definitely an attractive form of drug discovery. This has yielded new methods, some of which have been discussed, to identify new clinical uses for drugs that are either already in use or even those that have been shelved. Still, new computational pipelines are being developed to make sense of the big data which originates from various studies along the years. This will surely continue to augment the successes of drug repurposing.

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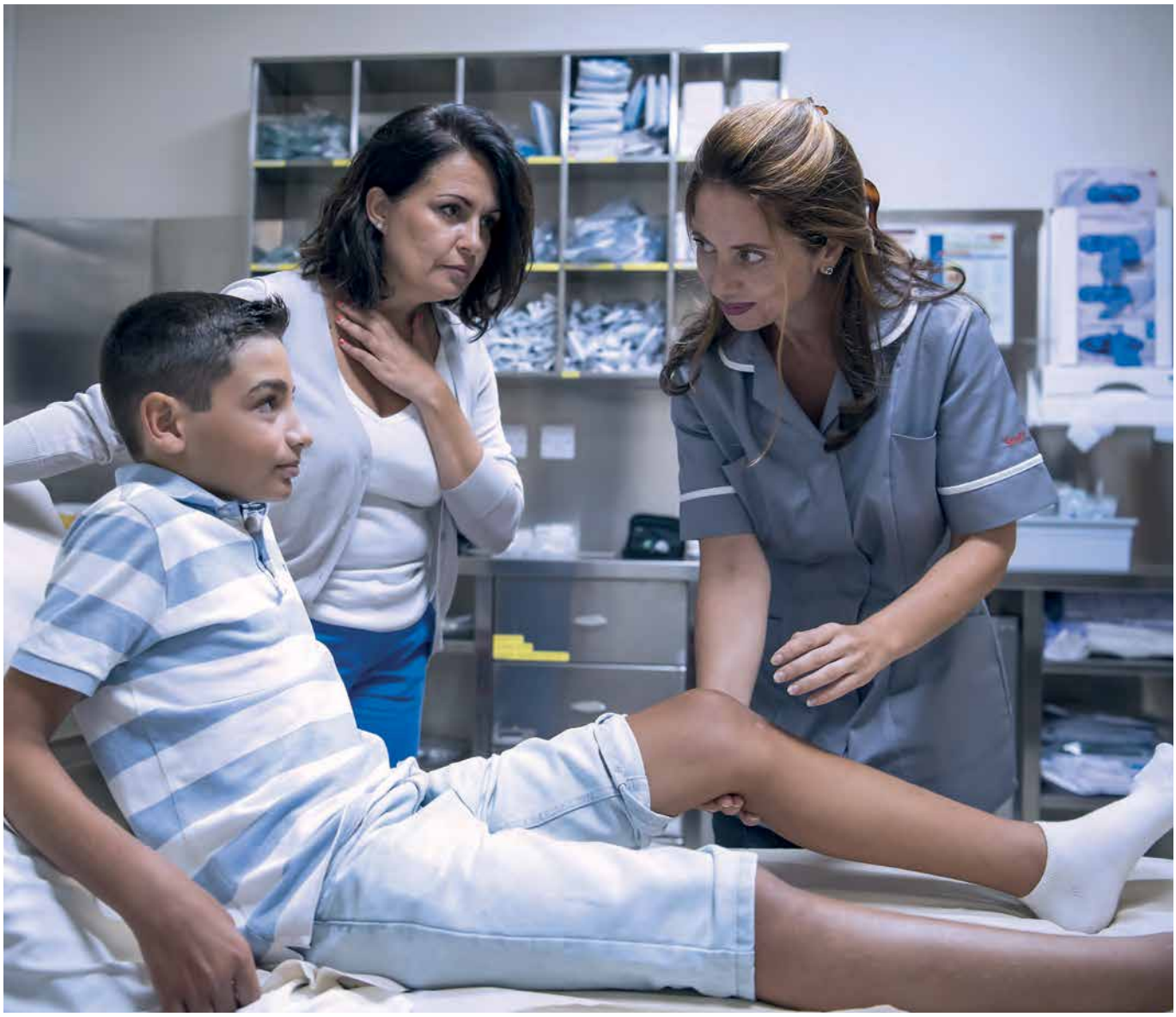

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