Management of Acute Liver Failure in Adults
The evolution of life expectancy in Malta over half a decade
Meeting Prof. Joseph Pace
The Dark Matter of the Genome: Some Insights and Clinical Applications
Actifed® oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders 1-7

**Actifed® DM COUGH LINCTUS**
- relieves dry cough and nasal congestion 3,6

**Actifed® SYRUP AND TABLETS**
- clears blocked and runny noses 2,5

**Actifed® EXPECTORANT**
- clears chesty cough and nasal congestion 4,7

### DOSAGE

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIQUIDS</strong></td>
<td></td>
</tr>
<tr>
<td>children aged 2 to 5 years 1-4</td>
<td>2.5ml every 4-6 hrs as required</td>
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<tr>
<td>children aged 6 to 11 years 2-4</td>
<td>5ml every 4-6 hrs as required</td>
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<tr>
<td>adults (including the elderly) and children aged 12 years and over 1</td>
<td>10ml every 4-6 hrs as required</td>
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<tr>
<td><strong>TABLETS</strong></td>
<td></td>
</tr>
<tr>
<td>adults (including the elderly) and children aged 12 years and over 1</td>
<td>1 tablet every 4-6 hrs as required</td>
</tr>
</tbody>
</table>

**OTC legal status applies for oral solutions in adults and children aged 12 years and over.**

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**ACTIFED ABREVIATED PRESCRIBING INFORMATION:** Please refer to full Summary of Product Characteristics (SPC) before prescribing. **TRADE NAME:** ACTIFED. **ACTIVE INGREDIENT:** Actifed DM Cough Linctus: Each 5ml contains Dextromethorphan Hydrobromide 10mg, Paracetamol Hydrobromide 30mg and Phenylephrine Hydrochloride 1 mg. Actifed Syrup: Each 5ml contains Paracetamol Hydrobromide 30mg and Phenylephrine Hydrochloride 1 mg. Actifed Tablets: Each tablet contains Paracetamol Hydrobromide 5mg, Phenylephrine Hydrochloride 5mg and Dextromethorphan Hydrobromide 1 mg. Actifed Expectorant: Each 5ml contains Theobromine Hydrobromide 1.5mg, Paracetamol Hydrobromide 30mg and Phenylephrine Hydrochloride 1 mg. **PHARMACOLOGICAL GROUP:** FORM: Oral solutions and Tablets. **INDICATIONS:** Symptomatic relief of upper respiratory tract disorders which are relieved by a combination of: Actifed DM Linctus, a mucous decongestant, an antihistamine and an antitussive; Actifed Syrup: a nasal decongestant, and an antihistamine; and an expectorant; Actifed Tablets: a nasal decongestant, and an antihistamine. **DOSE:** (See above). **CONTRAINDICATIONS:** Mindful that all new medicines approved for use are given a medical assessment as required by your doctor. **INTERACTIONS:** (See above). **ADVERSE EVENTS:** Cardiovascular system disorders or reactions with dizziness being reported most frequently; allergic dermatoses and rash. **REPORTING ADVERSE EVENTS (AEs):** If you become aware of any AEs, medication errors and/or use during pregnancy with GSK products, please report the event promptly to: GSK (Medicines) Limited, 1, De La Cruse Avenue, Gwamba GPM 2498, Malta (Tel: +356 21249801). Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system: Report forms can be downloaded from www.medicinesauthority.gov.mt and posted to the Malta Medicines Authority, Post-boxing Directorate, Level 3, Pria D’Argens, Gwamba GPM 1989, MALTA, or sent by email to postboxing@ medicinesauthority.gov.mt.

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References:
The US Presidential election will be held on 8 November 2016. There are two contenders, the billionaire 69-year old Donald Trump [Republican] and the millionaire 68-year old Hilary Clinton [Democrat]. Trump represents a conservative party and indeed seems to be more conservative than Clinton in all spheres. However, conservatives are facing a Hobson’s choice. The reason for this is that Trump seems to be the most liberal candidate in the party’s history. It has been rumoured that if Trump wins the election, the Republican Party will become essentially what the Democratic Party of the 1990’s was under Bill Clinton.

Representing two opposing parties, quite naturally, Clinton and Trump have divergent views on a number of key issues, one of which is the future of Obamacare. Whilst Clinton wants to improve Obamacare, Trump wants to repeal it. However, before proceeding further, it is important to illustrate the current state of affairs relating to healthcare in the US. One of the landmark reforms relating to healthcare which have been implemented in the US is the Patient Protection and Affordable Care Act, also known as Obamacare, which in 2010 reformed Medicare, the latter being in existence since 1966. Obamacare enacted a comprehensive system of mandated health insurance with its aim being extending health insurance coverage to those who lack it, including those people who receive no coverage from their employers, the poor and the elderly. To achieve its aims, Obamacare offers subsidies to make insurance coverage more affordable and also creates marketplaces - with websites similar to online travel sites - where individuals can compare prices as they shop for coverage. It aims to reduce the cost of insurance by enrolling younger (healthier) people into the insurance system. In addition, the law bans insurance companies from denying health coverage to people with pre-existing health conditions, allows young people to remain on their parents’ plans until 26 years of age, and expands the eligibility of the public health programme for the poor. It also requires companies with more than 50 full-time employees to offer mandatory health coverage. The law aims to eventually slow the growth of US healthcare spending, which is the highest in the world (as of 2013, excluding investment, health expenditure as a share of GDP was 16.4% for the US and an average of 9% for European countries).

Returning to the future of Obamacare, contrary to Clinton’s intention of strengthening and expanding Obamacare, in Trump’s plan for healthcare reform, he declares that he would repeal Obamacare since he deems it unconstitutional to oblige people to have a mandatory insurance. Trump’s vision also advocates [1] interstate sale of health insurance with a view to lower prices because of competition, [2] deducting health insurance premium payments from individuals’ tax returns similar to what businesses do and [3] price transparency from all healthcare providers, especially medics, clinics and hospitals. In tandem, Trump vehemently opposes the provision of healthcare to irregular immigrants, which he claims cost the US an annual $11 billion. The latter provision contrasts deeply with Clinton’s view since she seeks to expand access to affordable healthcare regardless of immigration status. Indeed, Clinton sponsored the Legal Immigrant Children’s Health Improvement Act of 2007.

Interestingly, both Clinton and Trump want government to negotiate with pharmaceutical companies to slash prices of medicines. This intention was heralded by the price hike of an old anti-parasitic drug Daraprim® (pyrimethamine). Although Daraprim® has been off-patent since the 1970s, following the acquisition of its marketing rights by Turing Pharmaceuticals in 2015, Turing increased the price from $13.50 to $750 per tablet. This was made possible because of the drug’s limited patient population, the absence of competing manufacturers, and a lack of therapeutic alternatives, effectively creating a monopoly. However, this turned the cost of prescription drugs into a political issue with health care analysts envisaging a catch 22 in the proposed governments’ intervention in pharmaceutical pricing … allowing the government to exert such influence could have unintended consequences, like suppressing drug company revenues which will inevitably cut back on research.

Notwithstanding the above, we are discussing politics after all, where candidates talk the talk but often, do not walk the walk. Despite all the confrontational drama with pharmaceutical companies, this industry continues to heavily finance candidates in their electoral run … to date, donating $7 million to presidential candidates in the 2016 presidential election, according to the Centre for Responsive Politics.

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.

Annual subscription rates outside Malta: Six issues €90 or equivalent, worldwide

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A maintenance bronchodilator treatment for patients with COPD who are breathless

Anoro® Ellipta® (umeclidinium bromide/vilanterol) Abridged Prescribing Information

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Kindly consult the full Summary of Product Characteristics (SmPC) before prescribing.

Trade Name: Anoro® Ellipta® Active Ingredients: 55 micrograms umeclidinium bromide and 22 micrograms vilanterol (as trifenatate). Pharmaceutical Form: 55 micrograms/22 micrograms inhalation powder, pre-dispensed. Indications: Maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (chronic obstructive pulmonary disease). Anoro® Ellipta® is not indicated for acute episodes of bronchospasm.

Contraindications: Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and magnesium stearate). Contraindications: Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and magnesium stearate). Contraindications: Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and magnesium stearate).

Precautions: Anoro® Ellipta® should not be used in patients with asthma. Treatment with Anoro® Ellipta® should be discontinued immediately in the event of paradoxical bronchospasm and alternative therapy initiated if necessary. Cardiovascular effects may be seen after the administration of muscarinic receptor antagonists and sympathomimetics therefore Anoro® Ellipta® should be used with caution in patients with severe cardiovascular disease. Anoro® Ellipta® should be used with caution in patients with urinary retention, narrow angle glaucoma, convulsive disorders, thyrotoxicosis, hypokalaemia, hyperglycaemia and severe hepatic impairment. No dosage adjustment is required in the elderly, in renal impairment or mild to moderate hepatic impairment. Acute symptoms: Anoro® Ellipta® is not indicated for acute episodes of bronchospasm.

Warn patients to seek medical advice if use of short-acting inhaled bronchodilator increases. A re-evaluation of the patient and of the COPD treatment regimen should be undertaken. Interactions with other medicinal products: Interaction studies have only been performed in adults. Avoid beta-adrenergic blockers since this may weaken or antagonize the effect of beta-adrenergic agonists. Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, telithromycin). Anoro® Ellipta® should not be used in conjunction with other long-acting muscarinic antagonists, long-acting beta-adrenergic agonists or medicinal products containing either of these agents. Caution is advised with concomitant use with methylxanthine derivatives, steroids or non-potassium-sparing diuretics as it may potentiate possible hypokalaemic effect of beta-adrenergic agonists. Fertility, pregnancy, and breastfeeding: No available data. Balance risks against benefits. Side effects: Common: Urinary tract infection, sinusitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, constipation and dry mouth. Uncommon: Atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles and rash. Legal category: POM. Presentation: Anoro® Ellipta®, 1 inhaler x 30 doses. Anoro® Ellipta® 55/22mcg. Marketing authorisation (MA) nos: 55/22mcg 1x30 doses (EU/174/888002); MA holder: Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex, TW8 9GE, UK. Last date of revision: October 2014. Anoro® and Ellipta® are registered trademarks of the GlaxoSmithKline group of companies. All rights reserved. Anoro® Ellipta® was developed in collaboration with Theravance, Inc.

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

REPORTING ADVERSE EVENTS (AEs):

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

Malta: alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:

Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D’Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

ANORO ELLIPTA was developed in collaboration with Theravance
A maintenance bronchodilator treatment for patients with COPD who are breathless should not be used in patients with asthma. Treatment with Anoro Ellipta magnesium stearate).

This medicinal product is subject to additional precautions. Anoro® Ellipta® (umeclidinium bromide/vilanterol)

Anoro should be discontinued immediately in the event of angioedema or anaphylaxis. Anoro® Ellipta® 55/22mcg.

Symptoms: Not specified

Anoro with caution in patients with severe cardiovascular disease.

Side effects:

Common:干咳, 头痛, 咽喉痛, 咽部或口腔疼痛, 恶心, 症状, 疲劳

Uncommon: 室性心动过速, 二度房室传导阻滞

Rare: 虚脱, 晕厥, 低血压

Anoro should be used with caution in patients with atrial fibrillation.

Precautions:

Anoro should be used with caution in patients with severe cardiovascular disease.

Anoro should not be used in conjunction with other long-acting muscarinic receptor antagonists and sympathomimetics therefore Anoro administration of muscarinic receptor antagonists and sympathomimetics should be discontinued immediately in the event of angioedema or anaphylaxis.

Avoid beta-adrenergic blockers since this may weaken the effect of beta 2-adrenergic agonists.

Cardiovascular effects may be seen after the administration of muscarinic receptor antagonists and sympathomimetics therefore Anoro administration of muscarinic receptor antagonists and sympathomimetics should be discontinued immediately in the event of angioedema or anaphylaxis.

As a pastime he cultivates bonsai trees and plays his sax also. The co-author of the article is Dr Michael Balzan.

Dr Godfrey Azzopardi MD FIAC is a resident specialist anaesthetist currently working at Mater Dei Hospital. In 2014 and 2015 he trained at the Intensive Care Department of the Austin Hospital in Melbourne Australia, which is a referral centre for liver failure. He is interested in specialising in intensive care.

Dr Kathleen England MD MSc is a consultant public health specialist within the Directorate of Health Information and Research. Her main areas of work and interest are health statistics and epidemiological research in health. The co-authors of the article are Prof. Tobias Vogl from the Max Planck Institute for Demographic Research, Germany and Dr Natasha Azzopardi Muscat from the Directorate for Health Information and Research.

Dr Michelle Muscat MD MICHELV MSc is currently in her third year reading for a PhD. In 2012 she obtained associateship of the Royal College of Pathologists (in chemical pathology). She harbours a strong interest in biochemical laboratory science.

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

Dr Mark Xuereb MD (Meija) MBChB(UK) MRCEM(UK) MMCFD (Meija.) is a UK-trained crisis psychiatrist. He was a clinical supervisor at Downing College, Cambridge University and lecturers locally in the Departments of Psychiatry and Gerontology. He presently leads crisis teams, being based at Mater Dei Hospital.
Forcid Solutab®:
- Contains amoxicillin and clavulanic acid in the ratio 7:1, the powerful combination to fight infections in unique Forcid Solutab® formulation

Forcid Solutab® indications:
- Acute bacterial sinusitis, acute otitis media, acute exacerbations of chronic bronchitis, community acquired pneumonia.
- Cystitis, pyelonephritis.
- Skin and soft tissue infections in particular cellulitis, animal bites.
- Severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Forcid Solutab® offers a convenient antibiotic therapy for adults and children:
- Easy and flexible administration, the unique formula can be swallowed intact or dissolved in water.
- Equally effective whether dissolved in water or taken as a tablet and rapidly absorbed.
- Suitable for a wide range of patients: no sugar, no gluten, no sodium, no lactose.

Forcid Solutab® dosing in adults and children ≥ 40 kg:
- Standard dose of Forcid Solutab 1000 is 2 times a day.
- For infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections, Forcid Solutab1000 is recommended to be given 3 times per day.

Forcid Solutab® contains amoxicillin and clavulanic acid in the ratio 7:1. The powerful combination to fight infections in unique Forcid Solutab® formulation.
THE DARK MATTER OF THE GENOME
SOME INSIGHTS AND CLINICAL APPLICATIONS

ALFRED GRECH & MICHAEL BALZAN

ABSTRACT
Only approximately 1.5% of the human genome encodes protein sequence; the rest is 'dark matter'. Research on these noncoding regions shows that they play roles in cellular homeostasis, development, differentiation and metabolism. Cancer, cardiovascular, developmental, and neurological diseases are characterised by aberrant expression of these regions. Exploring their clinical utility as biomarkers and molecular targets in medical theranostics is a very promising way forward.

INTRODUCTION
It is now well known that only approximately 1.5% of the human genome encodes protein sequence. However, comparative analyses with mammalian genomes have shown that at least 5% is under selective constraint and thus probably functional, of which approximately 3.5% consists of noncoding elements with apparent regulatory roles. Collectively, this created an aura of mystery, leading to the label of 'dark matter', in a manner analogous to the 'dark matter' of the universe, which we can neither easily detect nor understand, but that nonetheless exists and is open to experimental queries. Ongoing research on these noncoding regions, which form a major part of this once proverbial genomic 'dark matter', shows that they play vital biological roles in cellular homeostasis, development, differentiation and metabolism. Indeed, their aberrant expression is being found in a variety of human diseases, including cancer, cardiovascular, developmental, and neurological diseases. Consequently, translational research is exploring the clinical utility of these noncoding RNAs (ncRNAs) as biomarkers and molecular targets in medical theranostics.

THE DARK MATTER IN THE CLINIC
ncRNAs represent a significant portion of the human transcriptome. Based on their size, ncRNAs are grouped into two major classes, namely, small ncRNA and long ncRNA (lncRNA). microRNAs (miRNAs, approximately 22 nucleotides long) and transcription initiation RNAs (tRNAs, 18 nucleotides long) are two examples of the first class. In contrast, lncRNAs, which resemble mRNA transcripts, range from 200 nucleotides to approximately 100 kilobases. In humans, lncRNAs have been identified to be transcribed from four chromosomal regions, termed the Hox gene loci. These four Hox loci (Hoxa, Hoxb, Hoxc and Hoxd) include dozens of genes that are involved in a variety of biological processes, including embryonic development, cell differentiation and tumorigenesis.

Several lncRNAs are coded from regions between the genes in these Hox clusters, hence their other name being long intergenic non-coding RNA, or lincRNA. Increasing numbers of lncRNAs are being identified and their functions investigated. In fact, an emerging function is their role in genome modification, where they associate with Polycomb proteins to epigenetically silence genes. Specifically, this can occur through histone tail post-translational modifications, with methylation of histone H3 lysine 9 (H3K9me), lysine 27 (H3K27me), and histone H4 lysine 20 (H4K20me) being associated with regions of the genome that are transcriptionally inactive. Such silencing of genes through histone methylation is thought to be mediated by chromatin modelling complexes such as the Polycomb repressive complexes (PRC), PRC1 and PRC2. In this review, we will focus on what are perhaps the three most valued Polycomb-related lncRNAs in the clinical setting, i.e. ANRIL, HOTAIR, and XIST.
1. ANRIL

Spanning 126.3 kilobases in the genome, ANRIL is an antisense ncRNA in the INK4 locus. The INK4b (p15)–ARF (p14)–INK4a (p16) locus, which is found on chromosome 9p21, is said to be an essential regulator of cellular senescence. INK4 carries out this regulatory role by coding for three tumour suppressors i.e. p14 which increases p53 signalling, and p15 and p16, which (a) promote the function of the retinoblastoma protein pRB, and also, (b) inhibit cyclin-dependent kinases therefore causing cell cycle arrest. Regulation of the INK4 locus is governed by the Polycomb repressive complexes PRC1 and PRC2, where PRC2 initially trimethylates H3K27 in the transcriptionally silent heterochromatin, and then PCR1 recognises the methylated H3K27 as a sign to maintain the heterochromatin. Both cis- and trans-acting lncRNAs recruit Polycomb complexes to establish the heterochromatin. In this case, PRC1 and PRC2 are recruited to the INK4 locus by the lncRNA ANRIL, which is expressed antisense to the p14 and the p15 tumour suppressors.

It has been suggested that both Polycomb repressive complexes are recruited in cis to the INK4 locus gene through association with nascent ANRIL transcripts. Such a suggestion was made following results from a study showing that ANRIL knockdown leads to the upregulation of p15 and p16. Furthermore, the transcriptional state of the locus, which is often deleted or silenced in cancer, appears to be affected by changes in ANRIL expression.1 Upregulation of ANRIL is seen in prostate cancer tissues for instance,6 in heart disease, type 2 diabetes, and risk-associated single-nucleotide polymorphisms (SNPs) for cancers overlapping with the ANRIL region.7 One SNP in the 9p21 gene desert was also shown to be associated with coronary artery disease; this DNA variant disrupts the binding site for the STAT1 transcription factor which is known to repress the expression of ANRIL. Therefore, by stopping STAT1 from binding, it leads to the upregulation of ANRIL, and the cause behind coronary artery disease might well be the ANRIL-mediated silencing of p15.6 Similar to ANRIL is the lncRNA HEIH which was also found to regulate the INK4 locus, where by recruiting PRC2 to tumour suppressors, it facilitates hepatocellular carcinoma tumorigenesis.5

2. HOTAIR

HOTAIR is one of the recently identified lncRNAs. It is a 2,158-nucleotide-long, spliced and polyadenylated lncRNA, encoded by a 6,232 base pair gene, located in the Hoxc cluster on chromosome 12 (specifically at 12q13). Only one strand of HOTAIR, which is antisense to the canonical Hoxc genes, is transcribed; hence its name, standing for Hox Antisense Intergenic RNA.10 Unlike other documented lncRNAs that act strictly in cis (such as XIST), HOTAIR is the first lncRNA that is said to function in trans, because it is transcribed by one chromosome (chromosome 12), but regulates chromatin domains on another chromosome.11 HOTAIR exists only in mammals, has been highly conserved in primates throughout evolution, and has evolved faster than nearby HoxC genes. Poorly conserved sequences are present in its six exons, except for a 239 base pair domain in exon 6, which is particularly conserved.12

Presently, the proposed functional mechanism of HOTAIR is to act as a scaffold for the recruitment and binding of the Polycomb complex PRC2 and lysine-specific demethylase 1 (LSD1). PRC2 and LSD1 are multisubunit protein complexes that epigenetically modify chromatin. HOTAIR is believed to recruit these two complexes to regions of the genome so as to bring about gene silencing. For this reason, HOTAIR is emerging as an important player in tumorigenesis. It was found that high levels of HOTAIR are linked with metastatic spread and poor survival rate in breast cancer.13 Specifically, HOTAIR was shown to be highly upregulated in primary and metastatic breast tumours, even up to two-thousandfold over normal breast tissue. HOTAIR expression levels were also found to correlate with metastasis in colorectal cancer,15 gastrointestinal stromal tumours,16-17 hepatocellular carcinoma,16-17 and pancreatic cancer.18

The main challenge in introducing ncRNA-based therapeutics into clinical practice is the delivery and the off-target effects.
3. XIST

XIST, or X inactive specific transcript, is a mammalian lncRNA located in the X chromosome inactivation centre. Its gene product is first transcribed from the inactive X chromosome, and then, it spreads along the same X chromosome from which it was transcribed. In mammals, silencing of one of the two X chromosomes is necessary to achieve dosage compensation. The lncRNA XIST triggers X chromosome inactivation (XCI) in cells of the early embryo and in hematopoietic progenitors where silencing factors are present. XIST is not however required for the maintenance of XCI. XIST is also found to be expressed in adult females, and for this reason, it is suggested that the loss of XIST in adults could lead to the reactivation of inactive X genes. Having said this, the exact molecular mechanism by which XIST inactivates the X chromosomes remains unclear.

Nonetheless, surmounting evidence suggests that XIST has a role in the differentiation and proliferation of human cells. In fact, the dysregulated expression of XIST may play a pathologic role in cancer, which could be related to changes in gene expression, from the alterations to the stability of heterochromatin. It is possible that cancer cells produce silencing factors that allow for the inactivation of the X chromosome outside of the context of embryonic development. SATB1 (or special AT-rich sequence-binding protein-1), for instance, has been identified as a factor related to XIST-mediated chromosome silencing, and its aberrant expression was shown to promote breast, hepatocellular, prostate and other types of cancer. XIST silencing has also been reported in transgenic male fibrosarcoma cell lines, again suggesting a special context whereby X chromosome inactivation through XIST can occur in cancer cells.

**CONCLUSION**

ANRIL, HOTAIR and XIST are merely three of the ncRNAs that are currently being investigated. To mention but a few, others include Dleu2, EGO, IncRNA-a7, IncRNA-P21, and MEG3, each with an equal potential for being the missing piece of the puzzle. It is not therefore impossible to envisage a therapeutic world based on ncRNAs. Presently, however, the main challenge in introducing ncRNA-based therapeutics into clinical practice is the delivery and the off-target effects. Breakthroughs in both of these areas will pave the way forward for the future of medicine.
Mini Abridged Prescribing Information: Please refer to full Summary of Product Characteristics (SPC) before prescribing. TRADE NAME: Augmentin ES. ACTIVE INGREDIENTS: Amoxicillin (as trihydrate) and potassium clavulanate. PRESENTATION: 600 mg/42.9 mg/5 ml powder for oral suspension. Supplied in 100 ml glass bottle with a dosing spoon. INDICATION: treatment of acute otitis media and community acquired pneumonia infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant Streptococcus pneumoniae. POSOLOGY & ADMINISTRATION: Oral use. Recommended dose is 90/6.4 mg/kg/day in two divided doses. To minimise potential gastrointestinal intolerance, administer at the start of a meal. CONTRAINDICATIONS: Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. SPECIAL WARNINGS & PRECAUTIONS: Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Concomitant use of probenecid is not recommended. If co-administration occurs in patients receiving high doses or who have impaired renal function. Concomitant use of olsalazine may increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). INTERACTIONS: Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. Clinical monitoring should be performed during the combination with mycophenolate mofetil and shortly after antibiotic treatment. PREGNANCY & LACTATION: Use should be avoided unless considered essential by the physician. UNDESIRABLE EFFECTS: Very common (≥1/100, <1/10): diarrhoea. Common (≥1/100, <1/10): mucocutaneous candidosis, nausea, abdominal pain. Refer to SPC for full list of undesirable effects. AUTHORIZATION NUMBER: AA 1051/00101. MARKETING AUTHORISATION HOLDER: GlaxoSmithKline Bulgaria EOOD. LEGAL CATEGORY: P00A. DATE OF PREPARATION: July 2014. In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131). REPORTING ADVERSE EVENTS (AEs): If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi QRM 2458, Malta (Tel: +356 21238131). Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system: Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D’Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt.

References:  

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‘SURGICAL PATHOLOGY’ – WHAT’S IN A NAME?

Editor’s note: The Synapse is pleased to introduce a new series consisting of ‘Medical Anecdotes’... short accounts of interesting cases, some medical disasters, involving pathology and clinical practice, from the recollection of Prof. Albert Cilia-Vincenti.

The American name for ‘histopathology’ (also known as ‘cellular’, ‘tissue’ or ‘anatomic’ pathology) is ‘surgical pathology’, and there is medical history behind this label. In the 19th century, big American surgical departments were increasingly dissatisfied with reports from pathology colleagues. Surgeons were mainly interested in prognosis after excision of a diseased tissue or organ, and not in detailed microscopic descriptions devoid of any clinically useful information. They eventually decided that the pathological examination of their surgical specimens would be carried out in-house. This is why, in some of the larger American institutions, the surgical pathology department, including the frozen section room, is located within the surgical department.

These ‘novel concept’ surgical pathology departments immediately set about researching morphological clues to prognosis which, in the main, consisted of painstaking patient follow-up and histology review. One important breakthrough of this research was the identification of a group of pseudo-sarcomatous lesions. These mimicked sarcoma both clinically and microscopically. However, these pseudo-sarcomatous lesions had been responsible for many unnecessary limb amputations.

In the mid-1960s a Maltese medical student was suffering from a recurrent tumour in his right leg’s peroneal compartment muscles, which was diagnosed as fibrosarcoma. He struck it lucky when his Maltese surgeon declined to perform the indicated amputation himself and referred him to London’s Royal Marsden Hospital (previously called The Royal Cancer Hospital).

His luck consisted in that the pathologist at the Royal Marsden had just seen a paper by Arthur Purdy Stout, an American surgical pathologist, describing a number of pseudo-sarcomas, including a so-called “desmoid” tumour (now classified as ‘infiltrative fibromatosis’), and how to distinguish them microscopically from sarcoma. The paper detailed how these lesions were locally infiltrative like sarcoma but did not metastasize. Most of them occurred in the anterior abdominal wall muscles in women, apparently after pregnancy, and in limb muscles in both sexes, predominantly in the young, with a high recurrence rate after attempts at local excision, and a tendency not to recur further after increasing age.

The Maltese student had first noticed his leg tumour in his late teens and in total, had undergone four attempts at excising it, twice in Malta and twice in London. The latter two operations involved block dissections of lateral calf muscles, including excision of the fibula with the whole peroneal compartment muscles in the first of these operations. Recurrence did not occur after the fourth operation when he reached age 25. Many other young people have been spared limb amputations by the clinical research of American surgical pathologists.
Augmentin® SR
1000 mg/62,5 mg
Amoxicillin/Clavulanic Acid
Prolonged release tablets

✓ Unique bilayer tablet with immediate and sustained release delivery of amoxicillin provides superior efficacy against resistant pathogens\(^1,2\)

✓ Recommended by leading Guidelines in the treatment of Community Acquired Pneumonia\(^3,4\)

✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis\(^5\)

✓ Indicated for use in adults & adolescents aged ≥16 years; 2 tablets BD for 7-10 days\(^6\)

Spreading infectious livelihood!

Mini Abridged Prescribing Information: Please refer to full Summary of Product Characteristics (SPC) before prescribing. TRADE NAME: Augmentin SR. ACTIVE INGREDIENTS: Amoxicillin (as trihydrate) and potassium clavulanate. PRESENTATION: 1000 mg/62,5 mg prolonged-release tablets. Supplied in 28 tablet packs. INDICATION: Treatment of community acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant Streptococcus pneumoniae. POSSOLOGY & ADMINISTRATION: Oral use. Recommended dose of two tablets twice daily for seven to ten days, to minimise potential gastrointestinal intolerance, administer at the start of a meal. CONTRAINDICATIONS: Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. SPECIAL WARNINGS & PRECAUTIONS: Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains 29.3 mg (1.3 mmol) of sodium per tablet. Refer to SPC’s for full list of undesirable effects.

INDICATION
28 tablet packs.

PRESENTATION:
1000 mg/62,5 mg prolonged-release tablets. Supplied in
28 tablet packs. INDICATION: Treatment of community acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant Streptococcus pneumoniae. POSSOLOGY & ADMINISTRATION: Oral use. Recommended dose of two tablets twice daily for seven to ten days, to minimise potential gastrointestinal intolerance, administer at the start of a meal. CONTRAINDICATIONS: Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. SPECIAL WARNINGS & PRECAUTIONS: Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Contains 29.3 mg (1.3 mmol) of sodium per tablet. Refer to SPC’s for full list of undesirable effects.

References:
5. Augmentin SR SPC, April 2015.

Prepared: September 2015
Job No: MLT_GIB/AES/0002/15(2)
THE EVOLUTION OF LIFE EXPECTANCY IN MALTA OVER HALF A DECADE

KATHLEEN ENGLAND, TOBIAS VOGT AND NATASHA AZZOPARDI MUSCAT

ABSTRACT
An overview of life expectancy in Malta over the past sixty years shows a remarkable increase for both men and women. However, gains in life expectancy were not constant throughout the period. The rate of increase as well as the attributable causes of the noted increase varied over the years. Disparities in life expectancy by gender and by level of education exist. Life expectancy in Malta has caught up with Western Europe over the past 30 years and now compares well with the average for the EU-15. (The EU-15 consists of the 15 EU member states who became members in the European Union before 2004 and on average have the best life expectancies in the EU).

INTRODUCTION
The extension of the human lifespan has been significant in recent years, with world average life expectancy at birth having more than doubled over the past two centuries1 and rising by more than one-third in just the last four decades.2 Life expectancy is often used by countries as a measure of population health. It is an indicator that summarizes the mortality conditions in a country in a given year. Life expectancy at birth shows the number of years that a person can expect to live if current mortality conditions would prevail in the future.

The world average life expectancy for males stood at 69 years for males and 73 years for females in 20153 with highest average
Relvar Ellipta is for symptomatic treatment of patients with a FEV1 <70% predicted normal (post-bronchodilator) and an exacerbation history. For many patients like Joe with a history of exacerbations, COPD already takes up too much space in their life, yet they fear losing even more. So, when they need maintenance therapy, choose new Relvar Ellipta:

- The first ICS/LABA combination to deliver continuous 24-hour efficacy
- In a practical, once-daily dose
- Delivered in an easy to use device that patients prefer to their current inhaler

Controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. For COPD, one inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. Contraindications: Hypersensitivity to the active ingredient or excipients. Precautions for Use: Fluticasone furoate/ vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. Drug Interactions: Beta-blockers, CYP3A4 inhibitors, Poly(ethylene glycol) system with and symptomatic medicinal products (refer to the full Summary of Product Characteristics for full list of drugs). Fertility, Pregnancy and Lactation: Pregnancy: No adequate data available. Lactation: Insufficient information available. Fertility: There is no data in humans. Animal studies indicate no effect on fertility. Effect on Ability to Drive or Use Machines: No or negligible influence. Undesirable Effects: Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics). Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics).

For many patients like Joe with a history of exacerbations, COPD already takes up too much space in their life, yet they fear losing even more. So, when they need maintenance therapy, choose new Relvar Ellipta:

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- The first ICS/LABA combination to deliver continuous 24-hour efficacy
- In a practical, once-daily dose
- Delivered in an easy to use device that patients prefer to their current inhaler

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Please refer to the full Summary of Product Characteristics before prescribing.

Trade Name: RELVAR ELLIPTA. Active Ingredients: 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifluoroacetate). Pharmaceutical Form: 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispersed.

Indications: The 92 micrograms/22 micrograms dose for the regular treatment of asthma in adults and adolescents aged 12 years and older who use a combination medicinal product (long-acting beta agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV1,70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The 184 micrograms/22 micrograms dose: for the regular treatment of asthma in adults and adolescents aged 12 years and older who use inhalation powder, pre-dispersed.

Indications: The 92 micrograms/22 micrograms dose for the regular treatment of asthma in adults and adolescents aged 12 years and older who use a combination medicinal product (long-acting beta agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of adults with COPD with a FEV1,70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The 184 micrograms/22 micrograms dose: for the regular treatment of asthma in adults and adolescents aged 12 years and older who use a combination medicinal product (long-acting beta agonist and inhaled corticosteroid) is appropriate.

Dosing and Method of Administration: For Asthma: One inhalation of Relvar Ellipta 92/22 micrograms or 184/22 micrograms once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic. If symptoms arise in the period between doses, an inhaled, short-acting beta agonist should be taken for immediate relief. A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. For COPD, one inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day.

Contraindications: Hypersensitivity to the active ingredient or excipients. Precautions for Use: Fluticasone furoate/ vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, moderate-to-severe hepatic impairment, pulmonary tuberculosis or in patients with chronic or untreated infections, history of diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. Drug Interactions: Beta-blockers, CYP3A4 inhibitors, Poly(ethylene glycol) system with and symptomatic medicinal products (refer to the full Summary of Product Characteristics). Fertility, Pregnancy and Lactation: Pregnancy: No adequate data available. Lactation: Insufficient information available. Fertility: There is no data in humans. Animal studies indicate no effect on fertility. Effect on Ability to Drive or Use Machines: No or negligible influence. Undesirable Effects: Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics). Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics).
life expectancies by broad regions being attained in Europe and North America (Figure 1). In sharp contrast, life expectancy gains have been modest in Africa. In fact, due to the impact of AIDS, during the 1990s life expectancy actually decreased; however, since 2005 mortality due to HIV/AIDS has been decreasing, allowing life expectancy at birth to increase again.5

The original "epidemiological transition" theory by Abdel Omran was the first attempt to explain the progress in healthcare made by industrialised countries over the past two centuries. Further refinements of the original theory were made and are described as the stages of the 'health transition'.7 Between the turn of the 18th century and the 1960s, life expectancy improved dramatically from low levels of 30-35 years to reach about 70 years in the mid-1960s. This was primarily due to the reduction in mortality from infectious diseases. Improvements in living conditions, wealth and nutrition together with important public health measures including investment in safe drinking water and sewage systems were important measures responsible for major reductions in mortality from infectious diseases. This was followed by the introduction of immunisation and antibiotics. Since the 1970’s, we are experiencing a second stage in health transition relating to the reduction of cardiovascular disease, at least in high-income countries. More recently, some countries are now experiencing a third stage (possibly without having completed the previous one), which is the fight against ageing. However, these stages may occur at different times in different countries.7

IN MALTA — IT IS OF NOTE THAT THE GENDER GAP OBSERVED WITH LIFE EXPECTANCY DISAPPEARS WHEN CONSIDERING HEALTHY LIFE EXPECTANCY, INDICATING THAT THE ADDITIONAL LIFE EXPECTANCY IN FEMALES TEND TO BE LIVED WITH DECREASED HEALTH AND WITH ACTIVITY LIMITATIONS

THE SITUATION IN MALTA

An overview of life expectancy in Malta over the past 60 years has shown a steady increase (Figure 2), with life expectancy in 2014 reaching 79.97 for men and 84.37 for women.8 However, it is well known that substantial disparities in average life expectancy exist and these are associated with socio-economic variables. Persons who have higher levels of education have a higher life expectancy at birth compared to those with lower education levels. This gap is wider for men than women i.e. Males: least educated 77.30, most educated 81.80; Females: least educated 82.40, most educated 84.10, in 2011.9

Over the past 60 years, gains in life expectancy varied from one decade to another. Detailed demographic analysis of gains between 1955 and 1980 reveal that the gains are attributable mainly to a fall in infant mortality, as seen in figure 3. During this period, life expectancy in the older age groups actually deteriorated resulting in an overall picture of life expectancy stagnation in the 1970s. The largest gains in life expectancy were experienced during the 1980s with more modest gains being made in the 1990s. These gains are mainly observed in the older age groups and are largely attributed to the start of a downward trend in circulatory mortality (Figure 4).

Figure 3. Gains in life expectancy in Malta during the period 1957-2014 (age groups)

Figure 4. Trends in standardised mortality rate from circulatory diseases in Malta in males and females.5 SDR: Standardised Death Rate, M: Male, F: Female, MT: Malta.

Figure 1. Life expectancy at birth in 2014 by Broad World Regions.4

Figure 2. Trends in life expectancy in males and females in Malta.
HOW DOES MALTA’S LIFE EXPECTANCY TRAJECTORY COMPARE TO THE EU-15?

According to the data for 2014, the life expectancy for men (79.97) and women (84.37) in Malta compares well with that of EU-15 (life expectancy for EU-15 stood at 79.06 for males and 84.23 for females); however, this has not always been the case. Figure 5 shows how life expectancy for women in Malta has been persistently lower than that of EU-15 and only seems to catch up now. In men life expectancy improvement lagged behind in the 1970s but caught up in the latter half of the 1980s and has largely remained similar to the EU-15 since then.

A gender gap of around 4.5 years in life expectancy exists between men and women in Malta. This gap has remained relatively stable over the past 40 years. The gender gap in life expectancy varies substantially between different EU-28 member states with large differences between the sexes found in Lithuania (11.1 years in 2013), and smaller differences found in the Netherlands, United Kingdom and Sweden (3.7, 3.7 and 3.6 respectively).10

![Figure 5. Trends in life expectancy at birth in males and females in Malta compared to EU 15. LE: Life expectancy.](image)

**EXTREME LONGEVITY FOR MORE PEOPLE**

The current data for Malta shows that the oldest recorded female death occurred at 109 years and the oldest male death occurred at 106 years. In the 1950s, deaths in the 85 plus age group accounted for 5% in men and 8% in women. In 2014 they accounted for 23% and 43% of all deaths respectively.11 Moreover, the old age dependency ratio (represents the number of people aged 65 years and over per workers aged 15-64 years) increased from 12% and 13% in males and females respectively in 1955 to 23% and 31% in 2014. Whether extra years of life gained through increased longevity are spent in good or bad health is a crucial question. In this context indicators of health such as healthy life expectancy (HLE) are of increasing interest. HLE is defined as the number of years a person is expected to continue to live in a healthy condition (in absence of diseases or disabilities). In 2013, the HLE at age 65 was estimated at 12.7 years for females and 12.8 for males in Malta, well above the EU-28 average (8.6, 8.5 respectively).12 It is of note that the gender gap observed with life expectancy disappears when considering HLE, indicating that the additional life expectancy in females tend to be lived with decreased health and with activity limitations.

![Figure 5. Trends in life expectancy at birth in males and females in Malta compared to EU 15. LE: Life expectancy.](image)

**DISCUSSION AND CONCLUSIONS**

This article has described the evolution of life expectancy in Malta over the past sixty years. It has highlighted the gender differences as well as the periods that have contributed greatest to the gains to life expectancy.

Contributions to gains in life expectancy reach far beyond the health sphere alone. While recent advances in life expectancy, at least in high-income countries, were largely due to declines in mortality from circulatory disease, this appears to be dependent on their economic growth. Transmission of knowledge and technology for the control of circulatory diseases from higher to lower income countries in Europe does not suffice and the answer may lie in developing stronger and more equitable economic conditions.13

Gains in life expectancy in high income countries are resulting in an increase in the old age dependency ratio. In these countries ‘expected lifetime labour force participation as a percentage of life expectancy is declining’.14 As studies suggest that life expectancy will continue to increase in the years to come,15,16 countries facing such increase in longevity need to develop policies which will allow sustainable public pension and health care plans.

Notwithstanding this, not all countries have the same aging pattern, and migration of workers from younger, often poorer countries, to older, often richer countries, may serve to balance the global distribution of labour and capital.2

**REFERENCES**

Exacerbations
sudden worsening of COPD symptoms

Prevention
a key goal of long-term COPD care

Head-to-head study
Ultibro® Breezhaler®
dual bronchodilator (LABA/LAMA)
VS
Seretide®
bronchodilator and inhaled corticosteroid combination (LABA/ICS)

investigating the rate of COPD exacerbations
in people with an history of ≥1 exacerbation in the previous year

Ultibro Breezhaler

- met primary endpoint (non-inferiority)
- showed consistent superiority across exacerbation outcomes regardless of:
  - disease severity
  - eosinophil levels (a type of white blood cells)

- similar safety profiles

fewer cases of pneumonia

17% risk reduction
22% risk reduction

CONCLUSIONS
Ultibro Breezhaler is more effective than the current standard of care in reducing COPD exacerbations

These results are anticipated to impact the future care of people living with COPD

Seretide® (budesonide/fluticasone) 50/500 mcg is a registered trademark of the GlaxoSmithKline group of companies.

References
ULTIBRO® BREEZHALER

THE FIRST ONE-DAILY DUAL BRONCHODILATOR

Once-daily ULTIBRO BREEZHALER is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).”

ABSTRACT
Acute Liver Failure is a medical emergency characterised by cerebral oedema and non-convulsive seizures. Patients with fulminant hepatic failure need urgent workup for liver transplantation. In the meantime, a multimodal approach must be adopted to decrease the incidence of death from neurological complications.

INTRODUCTION
Acute liver failure is a rare, life-threatening condition. Often it occurs in young, previously healthy individuals. Management of these patients is extremely challenging. In view of the fact that experience in management outside specialised centres is limited, consideration for transfer to a tertiary centre with a facility for liver transplantation should be taken as early as possible. Management guidelines facilitate the standardisation of critical care management of these patients amongst different specialties, thereby promoting a smoother and more efficient continuity of care.

CLASSIFICATION OF ACUTE LIVER FAILURE
Liver failure is a triad of jaundice, coagulopathy and encephalopathy.

The O’Grady System classifies acute liver failure as:

1. Hyperacute: encephalopathy occurs within 7 days of the onset of jaundice;
2. Acute: encephalopathy occurs within 8 to 28 days of the onset of jaundice;
3. Subacute: encephalopathy occurs between 29 days to 12 weeks of the onset of jaundice.

PRESENTATION
Acute liver failure presents with acute, severe hepatitis, followed by coagulopathy (high INR) and encephalopathy. These patients typically lack the clinical and radiological signs associated with chronic liver disease, namely hepatomegaly, ascites, clubbing, leukoonychia, caput medusa, spider naevi, gynaecomastia and cirrhosis. Paracetamol overdose is the commonest cause of fulminant hepatic failure in developed countries, whereas viral hepatitis is the commonest cause worldwide. The development of cerebral edema is the main cause of morbidity and mortality in patients with acute liver failure.

PATHOPHYSIOLOGY OF CEREBRAL OEDEMA IN ACUTE LIVER FAILURE

1. HYPERAMMONAEMIA
Ammonia, a normal by-product of protein metabolism, is detoxified by the liver to urea. In liver failure, failure of hepatic ammonia metabolism leads to hyperammonaemia. In the brain, ammonia is converted to glutamine. In acute liver failure, this acute rise in intra-cerebral glutamine increases the osmotic pressure in astrocytes, leading to cerebral oedema. In chronic liver disease, the accumulation of intracerebral glutamine is more insidious. Hence, astrocytes have time to equilibrate to these osmolar changes and cerebral oedema does not occur.

2. MASSIVE SYSTEMIC INFLAMMATORY RESPONSE
This leads to cerebral vessel vasodilatation and increased vessel permeability. This promotes the shift of intravascular fluid to the interstitial space, thereby leading to cerebral oedema. In chronic liver disease, the systemic inflammatory response is much less pronounced.

INVESTIGATIONS OF ACUTE LIVER FAILURE
All patients presenting with acute, severe hepatitis of uncertain aetiology should undergo screening for viruses, autoimmune antibodies and toxins, including serum ethanol and paracetamol levels, and have a Doppler ultrasound of their liver. Patients with established acute liver failure should have 6 to 8 hourly blood tests, namely full blood count, serum electrolytes, renal profile, clotting profile, liver enzymes including serum albumin, serum ammonia and arterial blood gases. Serum phosphate levels should be monitored daily as phosphate is consumed during liver regeneration leading to hypophosphataemia. Since these patients are susceptible to infections, they should have regular blood, urine and sputum cultures.

MANAGEMENT OF ACUTE LIVER FAILURE

1. ORTHOTOPIC LIVER TRANSPLANT
Without liver transplantation, the prognosis is very poor in acute liver failure. Hence a hepatologist should be involved immediately,
even if the patients do not seem sick enough initially. These patients deteriorate very fast and may miss the therapeutic time window for surgery. There are no universal, exclusion criteria for liver transplantation. However, many specialised centres agree that patients who are very unstable (overt septic shock with multi-organ failure), have uncontrolled seizures or signs of impending brainstem herniation (fixed, dilated pupils or posturing movements) or have malignancies outside the liver will not benefit from liver transplantation. The American Society for Study of Liver Diseases has recommended the King’s College Criteria in assessing the need for liver transplantation in patients with acute liver failure. According to the King’s College Criteria, cases of paracetamol-induced acute liver failure should be referred for liver transplantation if they have:

1. pH < 7.3; or
2. INR > 6.5, serum creatinine > 300 μmol/L and Grade III/IV encephalopathy.

According to the King’s College Criteria, cases of non-paracetamol-induced acute liver failure should be referred for liver transplantation if they have:

1. INR > 6.5; or
2. Any 3 of the following: (a) age < 10 years or > 40 years; (b) aetiology - non-A, non-B hepatitis or idiosyncratic drug reaction; (c) duration of jaundice before encephalopathy > 7 days; (d) INR > 3.5; and (e) serum bilirubin > 300 μmol/L.

2. NEUROLOGICAL MANAGEMENT

The two most common neurological complications associated with acute liver failure are brain oedema and non-convulsive seizures. Intracranial haemorrhage due to coagulopathy is rare, but devastating when it occurs. All patients admitted with acute liver failure should have regular (30 minutes to 1 hourly) neurocharting. New, focal neurological deficits are more consistent with intracranial haemorrhage and warrant urgent CT brain. Symmetrical neurological deterioration with no focal deficits is more consistent with cerebral oedema. EEG is warranted in cases of neurological deterioration which cannot be explained by CT brain findings to exclude non-convulsive seizures, which would require treatment with intravenous anticonvulsants.

Brain oedema manifests clinically as severe confusion, somnolence and coma. Hence, all patients exhibiting any of these symptoms benefit from protective measures to restore cerebral perfusion, namely:

a. Measures to decrease brain oedema: including:
   i. Hyperosmolar therapy with hypertonic saline or mannitol aiming for serum osmolality of 310-320mOsm/L;
   ii. Renal replacement therapy to lower serum ammonia to < 60 μmol/L even in the absence of renal failure, as ammonia is cleared by dialysis;
   iii. Intubation and hyperventilation, aiming for PaCO₂ (arterial partial pressure of carbon dioxide) of 35mmHg. Cerebral blood flow is directly related to PaCO₂ up to certain limits. Hence, by decreasing PaCO₂, cerebral blood flow is reduced. Therefore, patients with clinical manifestations of intracranial hypertension benefit from intubation and controlled, mechanical ventilation even if their Glasgow Coma Scale > 8 and they are still able to protect their airway

b. Measures to promote cerebral venous drainage, namely head of bed elevation 30°, maintaining the head of intubated patients in the neutral position and avoiding any constrictive ties around the neck to fix the endotracheal tube.

c. Measures to promote cerebral arterial perfusion, namely:
   i. Hyperosmolar therapy with hypertonic saline or mannitol aiming for serum osmolality of 310-320mOsm/L;
   ii. Renal replacement therapy to lower serum ammonia to < 60 μmol/L even in the absence of renal failure, as ammonia is cleared by dialysis;

3. CARDIOVASCULAR SUPPORT

Patients with acute liver failure typically have high cardiac output states and vasoplosia. Noradrenaline is the vasoconstrictor of choice to counteract the vasoplosia. Restrictive fluid measures are usually desired to avoid worsening of cerebral oedema. These patients are prone to infections and septic shock as they are immunocompromised. Therefore, in case of non-improving clinical picture, broad spectrum antibiotics and antifungals should be considered early.

4. MANAGEMENT OF COAGULOPATHY

Coagulopathy is not corrected unless INR > 6 as it is a useful prognostic marker. Beyond this level, transfusion of fresh frozen plasma is indicated due to increased risk of spontaneous intracranial bleeding.

5. METABOLIC HOMEOSTASIS

Hypoglycaemia is common in acute liver failure as the hepatic glycogen stores are depleted. In such cases, hypertonic dextrose infusions should be used. 5% dextrose should be avoided as it worsens cerebral oedema.

6. N-ACETYLCYSTEINE INFUSION

In paracetamol overdose, hepatotoxicity occurs due to depletion of the hepatic glutathione stores. N-Acetylcysteine replenishes this hepatic glutathione. N-Acetylcysteine is also beneficial in non-paracetamol-induced acute liver failure as it has anti-oxidant properties and improves haemodynamics. In both cases, N-Acetylcysteine infusion should be commenced immediately and continued until discharge from intensive care or liver transplantation is performed.

CONCLUSION

A multimodal approach to the management of acute liver failure addresses the individual pathophysiological processes that occur in this condition. It improves chances of survival in patients awaiting liver transplantation and dramatically reduces the risk of death from neurological complications.

REFERENCE

Relvar Ellipta is for patients (≥12 years) in need of asthma maintenance therapy.

Because I simply don’t have space for asthma

For patients like Maria, every day is full on, so even small reminders of asthma can have an impact. So, when they’re uncontrolled on ICS alone, choose new Relvar Ellipta:

- The first ICS/LABA combination to deliver continuous 24-hour efficacy¹
- In a practical, once-daily dose¹
- Delivered in an easy to use device that patients prefer to their current inhaler[s]²,³

Relvar Ellipta (fluticasone furoate/vilanterol) Abridged Prescribing Information

This medicinal product is subject to additional monitoring. This will allow quick identification of any safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions. Please refer to the full Summary of Product Characteristics before prescribing.

Trade Name: RELVAR ELLIPTA. Active Ingredients: 92 micrograms or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifluoropropionate). Pharmaceutical Form: 92 micrograms/22 micrograms or 184 micrograms/22 micrograms inhalation powder, pre-dispensed.

Indications: The 92 micrograms/22 micrograms dose for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta agonist and inhaled corticosteroid) is appropriate; and for the symptomatic treatment of symptoms and that use should be continued even when asymptomatic. If informed that regular daily usage is necessary to maintain control of asthma improve lung function and/or to reduce the frequency of asthma exacerbations. The 184 micrograms/22 micrograms dose is appropriate.

Dosage and Method of Administration:

- For Athsma: One inhalation of Relvar Ellipta 92/22 micrograms once daily. Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. Relvar Ellipta is for inhalation use only. It should be administered at the same time of the day, each day. Contraindications: Hypersensitivity to the active ingredient or excipients. Precautions for Use: Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Caution in severe cardiovascular disease, metabolic and/or untreated infections, diabetes mellitus and for paradoxical bronchospasm and pneumonia in patients with COPD. Drug Interactions: Beta-blockers, CYP3A4 inhibitors, Polypropylene Glycol inhibitions and symphotametric medicinal products (refer to the full Summary of Product Characteristics for list of drugs). Fertility, Pregnancy and Lactation: Pregnancy: No adequate data available. Lactation: Insufficient information available. Fertility: There is no data in humans. Animal studies indicate effect on fertility, Effect on Ability to Drive or Use Machines: No or negligible influence. Undesirable Effects: Very common side effects include headache and nasopharyngitis (refer to the full Summary of Product Characteristics for list of undesirable effects). Overdose: There is no specific antidote. Treatment of overdose should consist of general supportive measures. Local Presentations: Relvar Ellipta 92/22 micrograms or 184/22 micrograms inhalation powder, pre-dispensed and Relvar Ellipta 184/22 micrograms/22 micrograms inhalation powder, pre-dispensed. Legal Category: POM. Marketing Authorisation Holder: Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom. Marketing Authorisation Numbers: EUT/13/286/001-6 DATE OF PREPARATION: December 2013

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21281813)

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1. Insuffi cient data available. 2. Insuffi cient data available. 3. Insuffi cient data available.
GERMAN MEASLES – WHY GERMAN?

German measles is also known as rubella, which is derived from Latin, meaning ‘little red.’ Rubella was initially considered to be a variant of measles or scarlet fever and was called ‘3rd disease.’ It was not until 1814 that it was first described as a separate disease in the German medical literature, hence the common name ‘German measles’. The virus is an enveloped, positive-stranded RNA virus classified as a Rubivirus in the Togaviridae family.

In 1914, the American physician Alfred Fabian Hess postulated a viral etiology for German measles based on his work with monkeys. The Japanese scientists S. Tasaka and Y. Hiro in 1938 confirmed the viral etiology by passing the disease to children using filtered nasal washings from persons with acute cases.

Following a widespread epidemic of rubella infection in 1940, Norman Gregg, an Australian ophthalmologist, reported in 1941 the occurrence of congenital cataracts among 78 infants born following maternal rubella infection in early pregnancy. This was the first published recognition of congenital rubella syndrome (CRS). Rubella virus was first isolated in 1962 by Parkman and Weller. The first rubella vaccines were licensed in 1969.

Rubella became notifiable under Maltese law in 1978, and legal provisions for the vaccination of girls between 10 and 13 years of age were mandated in 1989. Although CRS became notifiable in Malta in August 1990, only two cases were notified to the Department of Public Health till 1996.

BIBLIOGRAPHY


Mental Health

“’The mentally ill frighten and embarrass us. And so we marginalize the people who most need our acceptance. What mental health needs is more sunlight, more candor, more unashamed conversations’”

[Glenn Close, American actress, b. 1947]

Our society is changing at a very fast rate, however unfortunately, some of our attitudes are stuck to our roots. Mentally ill people are stereotyped and often discriminated against. Many people are woefully misinformed about mental health and thus it has become surrounded by ignorance, prejudice and fear.

The impact of stigma is twofold. Social stigma refers to prejudicial attitudes and discriminating behaviour towards individuals with mental health problems as a result of the psychiatric label they have been given, e.g. passing a negative remark about one’s mental condition and treatment. Subtle discrimination involves the avoidance of a person suffering from mental illness because it is assumed that the patient could be unstable. Self-stigma is the internalizing thoughts and silent fears which mental health sufferers go through due to their own perceptions of discrimination and perceived stigma, turning against themselves.

Therefore these patients are challenged doubly as they struggle with both the symptoms and complications that result from the disease and also the stereotypes and judgement that result from public humiliation and misconception about mental illness. This adds a greater burden, heavier to carry than the mental condition itself.

Mental illness can affect anyone, in different ways. The stigma and discrimination associated with mental health can be the hardest parts of the overall experience. Hence, we need to make a change in our daily judgemental comments and change them into positive vibes which bring happiness and courage to one another as one can never know what a person is going through.

Available Medical and Surgical Procedure Rooms

Medical and surgical procedure rooms are available for use in a state-of-the-art clinic in the most central part of B’Kara. Fully equipped, including sink, a/c and ample natural light. Nursing staff are available. Sharing reception facilities for appointments and all necessary amenities. For further enquiries please contact Mr. Jesmond Cilia on 99463738.
Seretide® Evohaler® 50 mcg from 4 years 2

Seretide® Diskus® 100 mg from 4 years 4

Help Poppy by prescribing Seretide

Seretide is the only ICS/LABA proven to achieve
guideline-defined asthma control in children 2

Safety Information

Very common side effects: Headache and nasopharyngitis.

Common side effects: Candidiasis of mouth and throat, pneumonia, bronchitis, hypokalaemia and hoarseness/dysphonia

Special warnings and precautions for use: Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids.

It is important that patients are reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained. Monitor height of children on prolonged inhaled steroid therapy.

References


Date of Preparation: January 2015

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studies, including initial funding issues as well as personal hardships. In the Phase I trial, cisplatin was used in combination with Herceptin©. Nicole, who had stage 4 cancer was the first patient to originally receive the drug during, what is called in the movie, the initial exploratory ‘mouse protein study’. This involved a single dose to test for tolerance in humans. However, she did not meet the eligibility requirements defined by the protocols for Phase I, and was hence not included in spite of the efforts by her relatives.

In the movie we see that the supraclavicular lump of a patient, enrolled in Phase I, noticeably decreases in size. On the other hand, one of the patients passes away due to her advanced cancer. These situations proved to be an emotional roller coaster for the cohort. Not all Phase I patients moved forward to Phase II, given the stringent Food and Drug Administration (FDA) standards for inclusion. During Phase III trials, the National Breast Cancer Coalition advocates were involved to allow compassionate access to the drug for the women who do not qualify for the trial. Towards the end of the movie, during the Revlon Run/Walk for women, Dr Slamon meets the relatives of some patients. The movie ends with the approval of Herceptin® by the FDA, which happened in 1998.

Although not shown in the movie, but directly related to the chemical pathology field of the author, a trastuzumab assay has later also been developed for the bioanalytical quantification of trastuzumab levels in blood. 

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REFERENCES

**TS: HOW LONG HAVE YOU BEEN A MEDICINE MAN?**

Next year I look forward to celebrating 50 years as a doctor. Over these years I have worked in Edinburgh, Manchester, Stoke-on-Trent, in Saudi Arabia, and of course in Malta. Here in Malta apart from my private practice which keeps me busy now, I held varied posts in the past including Chair of the Dermatology Department at Boffa Hospital and in the Faculty of Medicine from 1987-1990. I have also been President of the Medical Association of Malta, President of the World Medical Association, Chairman of the First EADV Spring Meeting held in Malta, and also President of the Foundation for Medical Services. I have been Secretary General of the European Academy of Dermatology for six years. Outside Europe I am Visiting Clinical Professor of Dermatology at Jefferson Medical Centre of Thomas Jefferson University in Philadelphia, and also a Fellow of the American Academy of Dermatology and the American Dermatology Association (ADA) besides being an Honorary member of several national Dermatology societies.

**TS: WHAT SKIN CONDITIONS HAVE INCREASED OVER THESE YEARS?**

Skin cancer and female adult acne. Everyone is or should be knowledgeable about skin cancer but in the past the latter was practically unheard of, indeed considered most unusual!! Today we see so many women in adulthood, suffering from what looks like teenage acne... and it may be linked to cysts in the ovaries (PCOS). If left untreated, this condition can have serious repercussions on other health issues. So the first alarm bell when a patient presents with adult acne is to consider possible PCOS. This condition can now be tackled from a young age, of great importance considering that patients with ovarian cysts may be prone to diabetes and heart disease.

**TS: WHAT ARE THE KNOWN CAUSES OF THIS?**

Stress is a major trigger, in adult acne as also in psoriasis and eczema. This skin condition causes enormous psychological damage. People think it is contagious, which it is not. This is in actual fact a hereditary condition which does become aggravated in stressful periods of life. In Malta, we unfortunately, (and some would say very unfairly) have a very ambiguous situation associated with support for manifestly chronic skin conditions. The Schedule 5 system rightly supports free medicines for chronic diseases. The problem is that it discriminates between equally chronic conditions and thus between equally affected and equally tax contributing Maltese citizens. Thus eczema patients get zero support while psoriasis patients get full support, in spite of both conditions seriously affecting Quality of Life confirmed objectively in numerous studies to be equal or worse than patients with chronic kidney and heart disease! There are many new treatments on the market, which, if made available, could alleviate much suffering for patients, including children, who may or may not be able to afford expensive treatment often for many years on a daily basis.
TS: HOW HAS MEDICINE CHANGED OVER THESE YEARS SINCE YOU GRADUATED?
I still remember when I became a doctor, we were still boiling needles. There were very few young doctors at the time. Now the hospital has large numbers of young doctors working within it. The modes of practise have changed completely - for one thing, the systems are all digitized now, including patients’ data. The hardware, the techniques … so much has transformed medicine. However, we must never forget the dictum of the late Professor Ganado who referred to His Majesty the patient or that of the Knights of Malta - Our Lords the Sick.

TS: WHEN YOU ARE OUT AND ABOUT DO YOU EVER STOP AND NOTICE PEOPLE WITH TERRIBLE OR POSSIBLY DANGEROUS SKIN CONDITIONS AND WOULD YOU POINT IT OUT TO THEM?
It is very difficult because yes, I do notice people with skin cancer or terrible acne. Some things just jump to attention for somebody like myself who has been treating skin problems for so long especially if these can be improved. One has to be very careful not to alarm people, and not to interfere with their privacy. However, there have been situations where I could not fail to note a dangerous skin lesion, in which case I did throw a very diplomatic hint that it would be wise to have it seen to sooner rather than later.

TS: WHAT DO YOU DO WHEN YOU ARE NOT TREATING PATIENTS?
I have been deeply involved in medical politics both here and abroad. I have a very full family life which includes five grandchildren, who I refer to as a lovely granddaughter and four terrorists! Everybody knows that I am a football fan … actually an ardent Juventus football fan who at long last this year managed to obtain a season ticket and saw 12 games, all wins: what an experience.

TS: HOW DID THIS LOVE FOR THE JUVENTUS TEAM COME ABOUT?
I always liked the team, was always a fan. 30 years ago I was in Brussels to attend the European Cup Final between Juventus and Liverpool. It was the 29 May 1985, a date I will never forget. So many Juve fans died or were injured when a wall collapsed in the Heysel Stadium. I was there with the crowd and well … after something like that, the bond only became stronger. It is incredible that one dies at a football match.

I READ THE SYNAPSE BECAUSE…
perhaps it is the only way to keep up with local happenings although the editor rightly steers clear of controversy. He does a great job and has a great team …
Just last month, Jane was a prisoner in her own home.

Serotonergic antidepressants insufficiently address the core depressive symptoms associated with “Decreased positive affect”

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

WELLBUTRIN XR – Abbreviated Prescribing Information: Please refer to full Summary of Product Characteristics (SmPC) before prescribing. TRADE NAME: Wellbutrin XR modified release tablets. COMPOSITION: Bupropion Hydrochloride 150 mg and 300 mg. INDICATIONS: Treatment of major depressive episodes. POSOLOGY AND METHOD OF ADMINISTRATION: Wellbutrin XR tablets should be swallowed whole and not crushed or chewed as this may lead to an increased risk of adverse events including seizures. Adults: The recommended starting dose is 150 mg once daily; if no improvement is seen after 4 weeks the dose may be increased to 300 mg once daily. There should be an interval of at least 24 hours between successive doses. Children and Adolescents: Not indicated for use in children or adolescents aged less than 18 years. Elderly Patients: Same as adults but with greater sensitivity in some elderly individuals. Hepatic and renal impairment: 150 mg once a day. Discontinuing therapy: A tapering off period may be considered. Overdose: Symptoms including drowsiness, loss of consciousness and/or ECG changes and rarely deaths even with large overdoses. CONTRAINDICATIONS: Hypersensitivity to bupropion or any of the excipients; co-administration with other medicinal products containing bupropion as the incidence of seizures is dose-dependent; current seizure disorder or history of seizures; known CNS tumor; withdrawal from alcohol or any medicinal product known to be associated with “Decreased positive affect”;1 associated with “Decreased positive affect”1 Serotonergic antidepressants should be reduced when given concomitantly with Wellbutrin XR. Use with caution with cyclophosphamide and ticlopidine, carbamazepine, phenytoin, ritonavir, tamoxifen, valproate, levodopa or amantidine, alcohol and nicotine transdermal system. ADVERSE EVENTS: Very Common: Insomnia, headache, dry mouth, gastrointestinal disturbance including nausea and vomiting. Common: Hypersensitivity reactions such as urticaria, anorexia, agitation, anxiety, tremor, dizziness, taste disorders, visual disturbance, tinnitus, increased blood pressure (sometimes severe), flushing, abdominal pain, constipation, rash, pruritus, sweating, fever, chest pain and asthenia. Not known: suicidal ideation and suicidal behaviour. Refer to the SPC for a full list of adverse events. PREGNANCY AND LACTATION: Not recommended. ABILITY TO DRIVE AND USE MACHINES: Use with caution. PRESENTATIONS: Wellbutrin XR 150 mg and 300 mg x 30 tablets. LEGAL CATEGORY: POM. Marketing Authorisation Holder: Glaxo Group Limited, UK. Marketing Authorisation Number: MA 302/00171-2. Date of preparation: September 2013. In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

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REPEITITIVE TRANSCRANIAL MAGNETIC STIMULATION—
A REVOLUTIONARY TREATMENT FOR DEPRESSION
AND OTHER DISORDERS

Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe, painless, effective and natural evidence-based treatment for people suffering from severe unipolar affective/depressive disorder and other neurological/psychological illnesses. Used successfully in renowned centres such as the Mayo clinic, Johns Hopkins and the Nottingham Neurormodulation Unit, rTMS is now available locally. This non-invasive FDA and NICE approved electromagnetic therapy is ideal for depressed patients who are either resistant or intolerant to other treatments. rTMS has no side-effects associated with drugs (e.g. weight gain, sexual dysfunction, sedation). Besides, no anaesthetic is involved and there is no memory loss or impaired learning as may happen with electroconvulsive therapy (ECT), which has long been considered the gold standard for treating such patients. rTMS is claimed to be more effective than medication, psychotherapy or ECT in treatment-resistant patients. Thankfully, rTMS has a synergistic effect when used with other treatments.

WHO states that there are 350 million depressed people worldwide. Depression is the leading cause of disability globally. When coupled with other co-morbid illnesses, it has a lifetime prevalence of 23%. The hidden psychological and social burden inherent to depression causes many to suffer in silence, potentially leading to suicide. Furthermore, for every person who commits suicide there are at least 20 others who try. rTMS can give relief to these people, prevent deaths and offer hope to those suffering from e.g. migraine, ADHD, altered body image, OCD.

rTMS is the brainchild of Baker and his colleagues who began experimenting in the 1980s. Inspired by Galvani and Aldini’s eighteenth century experiments on electrically stimulating the peripheral muscles of dead animals and corpses respectively, the UK team pioneered the stimulation of the human brain’s motor homunculus electromagnetically. Their objective at the time was to elicit a corresponding motor stimulation of peripheral muscles.

In 1987, Bickford extended the domain of TMS research into neuropsychiatry. He described transient mood elevation in healthy subjects receiving single-pulse stimulations to the motor cortex. This was the turning point for the scientific investigation of the effects of depolarising magnetic neuropathic disorders. Technological developments produced repetitive-pulse TMS which was shown to have long lasting effects on the cortex that persisted beyond the stimulus delivery. Once it was ascertained that rTMS technology could stimulate the brain in a focal way, the search was on to use this technique to treat neuropsychiatric disorders, with the earliest studies attempting to treat depression.

This novel treatment is based on the discoveries of British nineteenth century physicist Michael Farady, whose Law of Electromagnetic Induction predicts how a changing magnetic field will interact with an electric circuit to produce an electromotive force - a phenomenon called electromagnetic induction.

In essence, exposing a conductor to a rapidly changing magnetic field will induce a current in the conductor. rTMS works by inducing a rapidly changing magnetic field in a “depression sensitive” brain/cortical area, which is populated by neurons and is located just under the skull. This rapidly changing field induces a current in the neurons (the conductor). Hence, the area is stimulated to be more electrically active.

In biophysiological terms, several studies show that the left dorso-lateral pre-frontal cortex (LDLPC) along with deeper cortical structures such as the limbic system, is associated with mood regulation and hence is a lymphkin in the pathogenesis of depressive illness. Overall, a depressed brain is less active than a healthy brain, as evidenced by several neuroimaging studies. It also has fewer brain receptors, less circulating neurotransmitters (e.g. serotonin) and fewer healthy nerve contacts (synaptic connections between neurons).

rTMS addresses this neuronal “apathy” by progressively re-stimulating a current in the LDLPC neurons (i.e. a wave of depolarisation down the neuron membranes) so as to eventually restore the balance of neurotransmitters and healthy nerve contacts. The positive behavioural effects of this technology persist after a course of rTMS treatment.

NICE “noted consistently positive outcomes in many studies” and explained that rTMS has “a good safety profile”. Besides, “commentary from patients was positive and described significant benefits to their quality of life, including the advantages, for some patients, of being able to stop the use of oral antidepressant medications”.

In essence, the patient is seated in a comfortable chair as an electromagnetic field is applied over the LDLPC for up to 37 minutes. Patients remain fully alert throughout: no anaesthetic, medicine or invasive procedure is required. During the session, the person can talk, read or watch TV. He can even undergo psychotherapy. Once done, the patient simply hops off the chair and carries on with his day.

If your patients feel life is not worth living, please reassure them that it is! However, they may be going through a crisis. We can help. Call us on our 24/7 crisis line (99339966), email us (crisismalta@gmail.com) or get help from our Crisis Resolution Malta FaceBook page.
Back Support

Dynacross
Lambar- Abdominal Support
- Low back pain
- Moderate activity
- Moderate pain

Lambocross
- Functional Muscle Stimulation
- Surgically corrected or otherwise

Ortelcross
- Low back pain
- Moderate pain
- Moderate activity

Stomex
- Post operation support
- For stoma patients
- Can be cut through

Ortel
- Hernia belt
- Right, left, or bilateral adjustment

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A smarter approach to your health & wellbeing
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During pelvic ultrasound (US), the examiner consistently reports findings in the uterine body, endometrium and adnexa, while the cervix is often not mentioned. This probably results from a training in transabdominal pelvic US, since the cervix is poorly seen with this technique. On the other hand, endovaginal pelvic US with the excellent image quality obtainable on new devices, allows detailed assessment of the cervix.

Endovaginal US can visualize the cervix in both the long axis and the short axis. The long axis lies parallel to the cervical canal, which extends from the internal os to the external os. In the long axis of the cervix, a central echogenic line is seen that correlates with the apposed surfaces of the anterior and posterior mucosal (or glandular) layers that line the cervical canal. A small amount of fluid may be present within the cervical canal particularly in the periovulatory period. The mucosal layer, which lines the cervical canal, is iso- to hyperechoic and measures 2-4mm in thickness. Surrounding the mucosal layer is the stromal layer, which is moderately echogenic and forms the bulk of the cervix. Between the mucosal and stromal layer, a thin 1-2mm hypoechoic line may be seen that represents the submucosal layer (Figure 1).

Endovaginal US in the short axis shows the cervix as round or oval, containing a central echogenic spot representing the cervical canal surrounded by an iso- to hypoechoic mucosal layer, which is in turn surrounded by the echogenic stromal layer. Frequently, folds may be seen in the mucosal layer that represent the plicae palmatae (Figure 2).

Magnetic resonance imaging (MRI) allows the best visualization of the cervix and is used to characterize indeterminate US abnormalities. MRI is the gold standard for staging cervical cancer. On T2-weighted images, the cervix shows a distinctive trilaminar appearance, with an innermost hyperintense layer measuring 3–8 mm that corresponds to

Figure 1. Endovaginal US scan in the long axis of the cervix at 15-week gestation showing a central echogenic line that represents the apposed surfaces of the cervical mucosa (white arrow), surrounded by the mucosal layer (black arrow) and stromal layer (S). A thin hypoechoic submucosal layer lies between the stromal and mucosal layers (arrowhead).

Figure 2. Endovaginal US scan in the short axis of the cervix showing the mucosal layer (arrows) and the stromal layer (S). Plicae palmatae are present in the mucosal layer (arrowheads).
mucosa and secretions, a middle low-signal-intensity layer representing the inner cervical stroma that measures 3–8 mm, and an outermost intermediate-signal-intensity layer representing the outer cervical stroma that measures 2–8 mm (Figure 3).

Figure 3. MRI scan of the cervix in longitudinal section showing the mucosal layer (arrowheads), the inner stromal layer (arrows) and the outer stromal layer (curved arrow).

CONGENITAL ANOMALIES

Congenital anomalies of the cervix are readily seen on US but are best demonstrated on MRI. One of the most common congenital anomalies is a septate uterus and cervix accounting for circa 45% of all congenital uterine anomalies. This results from incomplete fusion of the Müllerian ducts with persistence of an intervening septum. On US, it is best visualized in the coronal plane as a hypoechoic band extending from the uterine fundus into the cervix (Figure 4). The septum is composed mainly of fibrous stroma, which accounts for its hypoechogenicity. It shows increased vascularity on colour Doppler US in 70% of cases. MRI is the best imaging modality to evaluate a septate uterus and cervix; the fibrous septum is depicted as a low signal band extending from the flat uterine fundus into the cervix in the coronal plane (Figure 5). The septum may continue into the vagina in up to 25% of cases.

Uterus didelphys or “Double Uterus” represents a congenital anomaly where there is complete duplication of the endometrial cavity. The two endometrial cavities are separated not just by a fibrous septum as in a septate uterus but by a central stromal layer lined on either surface by mucosal layers. A uterus didelphys may contain two separate uterine cavities fusing into a single cervical canal or a fully duplicated cervix (Figure 6a). It may be difficult to distinguish a septate cervix from a duplicated

Figure 4. Coronal endovaginal US of the uterus and cervix showing a midline septum extending from the fundus (arrowheads) into the cervix (arrow). Note the flat shape of the fundus, a feature which is used to differentiate a septate from a bicornuate uterus (+internal os).

Figure 5. Coronal T2 weighted MRI images of the uterus (a) and cervix (a and b). A hypodense septum (arrows in a and b) extends from the flat fundus (arrowheads in a) into the cervix. Case courtesy of Dr Aneesh km, Radiopaedia. org, ID: 27061.
DUAC (CLINDAMYCIN/BENZOYL PEROXIDE) IS AN EFFECTIVE TREATMENT THAT HELPS YOUR MILD TO MODERATE ACNE PATIENTS TO SEE IMPROVEMENTS FAST1,3

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

DUAC UNDERSTANDS WHAT’S IMPORTANT TO PATIENTS

• Duac works fast, starting to work in just 2 weeks3
• Duac is a once daily treatment2
• Duac is generally well-tolerated2,5

DUAC INDICATIONS & USAGE ADVICE2

• Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above2
• Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability2

YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE
Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance4:
Once-daily, in the evening, your patients should2:

1. Thoroughly wash the affected area of skin
2. Gently pat dry
3. Apply a thin layer of Duac gel on the affected area, not just the individual spots

TIPS4
If your patient’s skin peels or becomes dry, they can try:
• Using an oil and fragrance-free hypoallergenic moisturiser
• Using Duac less often, or stopping for one or two days before starting again

DUAC HAS A DUAL MODE OF ACTION2

Benzoyl Peroxide  Clindamycin

• Keratolytic2
• Treats comedones2 and inflammatory lesions2
• Bactericidal action against P. acnes strains2

• Suppresses P. acnes 2
• Anti-inflammatory action2

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

DUAC UNDERSTANDS WHAT’S IMPORTANT TO PATIENTS

• Duac Once Daily 10mg/g + 50mg/g Gel Abridged Prescribing Information

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

Trade Name: DUAC® ONCE DAILY GEL. Active Ingredients: Clindamycin phosphate/ anhydrous benzoyl peroxide. Pharmaceutical Form: 10mg/g + 50mg/g gel. Indication: Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. Posology and Method of Administration: Cutaneous use only. Adults and Adolescents: Once daily in the evening. Treatment should not exceed more than 12 weeks. Elderly: No specific recommendations. Contraindication: Hypersensitivity to active substances, lincomycin and any of the excipients. Precautions for Use: Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated/broken skin. Use with caution in patients with a history of regional enteritis, ulcerative colitis and antibiotic-associated colitis. If significant diarrhoea occurs or patients suffers from abdominal cramps, treatment should be immediately discontinued. Resistance to clindamycin: Patients with a recent history are more likely to have pre-existing anti-microbial resistant Propionibacterium acne and commensal flora. Cross-resistance: May occur when using antibiotic monotherapy. Fertility, Pregnancy and Lactation: There is no adequate data. Avoid application of the product to the breast area. Effect on Ability to Drive or Use Machines: No studies. Side Effects: Very Common side effects (at least 1 in 10) include erythema, peeling and dryness. Common side effects (less than 1 in 10) include burning sensation, photosensitivity and headache. Overdose: No specific antidote. Treatment should consist of appropriate symptomatic measures or clinically managed.


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Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/
cervix on ultrasound; in a duplicated cervix the band separating the two cervical canals is thicker than in a septate cervix (Figure 6b). Figures 6c and d illustrate separate endometrial cavities and cervical canals with a band of intervening stroma, clearly shown on MRI (Figure 6c and d).

**CERVICITIS**

Cervicitis is the term used to describe cervical inflammation, which may be acute or chronic. This is most often caused by infection, although trauma, pelvic radiation, chemical irritation, and sometimes malignancy may also cause cervical inflammation. Microorganisms such as *Trichomonas vaginalis*, *Candida albicans*, herpes simplex virus (especially type 2), *Neisseria gonorrhoeae* and *Chlamydia trachomatis* can also cause cervicitis. Patients usually present with purulent cervical and vaginal discharge and may complain of pelvic discomfort. US findings of cervicitis can be subtle or even completely occult, especially if the condition is of a chronic nature or if the patient is examined during or after effective antimicrobial treatment. At US, the cervix in patients with acute cervicitis shows a diffusely heterogeneous echotexture of the cervical mucosa and stroma (Figure 7a), with markedly increased vascularity on Doppler US imaging (Figure 7b). Hypervascularity can also be seen in cervical carcinoma, however in cervicitis, no mass lesion is seen. Cervicitis may lead to cervical canal stenosis and complex fluid collections within the cervical canal. Such fluid collections may mimic a cystic tumour in the cervical canal on US, however colour Doppler evaluation would confirm the avascular nature of the endocervical content (Figure 8).

![Figure 6. Diagram (a) showing a uterus didelphys with complete duplication of the cervix and a vaginal septum. US transverse scan (b) showing a duplicated uterine cavity (arrows). Short axis T2-weighted MR images showing duplication of the uterine cavity (arrows in c) and of the cervix (arrows in d) in a uterus didelphys. Case courtesy of Prof Frank Gaillard, Radiopaedia.org, rID: 11115.](image)

![Figure 7. Sagittal US scans in a case of cervicitis showing heterogeneity of the mucosal layer (arrows in a) with marked hypervascularity on colour Doppler US (b).](image)

![Figure 8. Sagittal US scan showing a complex fluid collection in the cervical canal; note the presence of plicae palmatie (arrows) as well as the absence of colour Doppler flow signal within the cervical canal.](image)
Nabothian cysts are one of the most common findings on pelvic ultrasound. Nabothian cysts are mucus-retention or epithelial-inclusion cysts that arise from an obstruction of endocervical glands by proliferating squamous epithelium. They may or may not be associated with previous clinical or subclinical episodes of cervicitis. Nabothian cysts may appear as anechoic fluid collections in the mucosal layer of the cervical canal (Figure 9a), but can be quite large and protrude into the stromal layer (Figure 9b). They may also contain echogenic material due to secondary intracystic haemorrhage (Figure 9c) and even calcifications (Figure 9d).

Cervical polyps are the most common endocervical lesions and are also the most common cause for intermenstrual bleeding. They occur most commonly in women between the ages of 30 and 40 years of age and 25% are associated with an endometrial polyp. Cervical polyps appear slightly hyperechoic compared to the cervical mucosa on US (Figure 10a), they are seen to move on pressure with the endovaginal probe and are frequently noted to have a vascular pedicle on colour Doppler US (Figure 10b).

Cervical fibroids or fibromyomas are not uncommon and may lead to some diagnostic difficulty. They may also result in shoulder impaction during child birth. Cervical fibroids are seen as hypoechoic mass lesions in the cervical stroma (Figure 11a). MRI is the most reliable modality to confirm the diagnosis, which shows low signal on all imaging sequences (Figure 11b).

The second part of this article will discuss imaging of endometriosis in the cervical canal and also cervical cancer. The importance of imaging in staging of cervical cancer will be presented.
Prescribing Information

Presentation: Betmiga™ prolonged release tablets containing 25 mg or 50 mg mirabegron.

Indication: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Dosage: Adults (including the elderly): Recommended dose: 50 mg once daily. Children and adolescents: Should not be used.

Contraindications: Hypersensitivity to active substance or any of the excipients. Should not be used in patients with end stage renal disease, severe hepatic impairment and severe uncontrolled hypertension. Not recommended in patients with severe renal impairment and moderate hepatic impairment concurrently receiving strong CYP3A inhibitors. Dose adjustment to 25 mg is recommended in patients with moderate renal and mild hepatic impairment receiving strong CYP3A inhibitor concomitantly. Caution in patients with a known history of QT prolongation or in patients taking medicines known to prolong the QT interval. Not recommended during pregnancy and in women of childbearing potential not using contraception. Not recommended during breastfeeding. Caution in patients with a known history of QT prolongation or in patients taking medicines known to prolong the QT interval. Not recommended during pregnancy and in women of childbearing potential not using contraception. Not recommended during breastfeeding.

Interactions: Clinically relevant drug interactions between Betmiga™ and medicinal products that inhibit, induce or are a substrate for one of the CYP isozymes or transporters are not expected, except for inhibitory effect on the metabolism of CYP2D6 substrates. Betmiga™ is a moderate and time-dependent inhibitor of CYP3A. No dose adjustment needed when administered with CYP2D6 inhibitors or CYP2D6 poor metabolisers. Caution if co-administered with medicines with a narrow therapeutic index and significantly metabolised by CYP2D6. When initiating in combination with digoxin the lowest dose for digoxin should be prescribed and serum digoxin should be monitored.

Adverse Effects: Urinary tract infection, tachycardia, palpitation, atrial fibrillation, blood pressure increase, leukocytoclastic vasculitis. Prescribers should consult the Summary of Product Characteristics in relation to other side effects.