# THESYNAPSE

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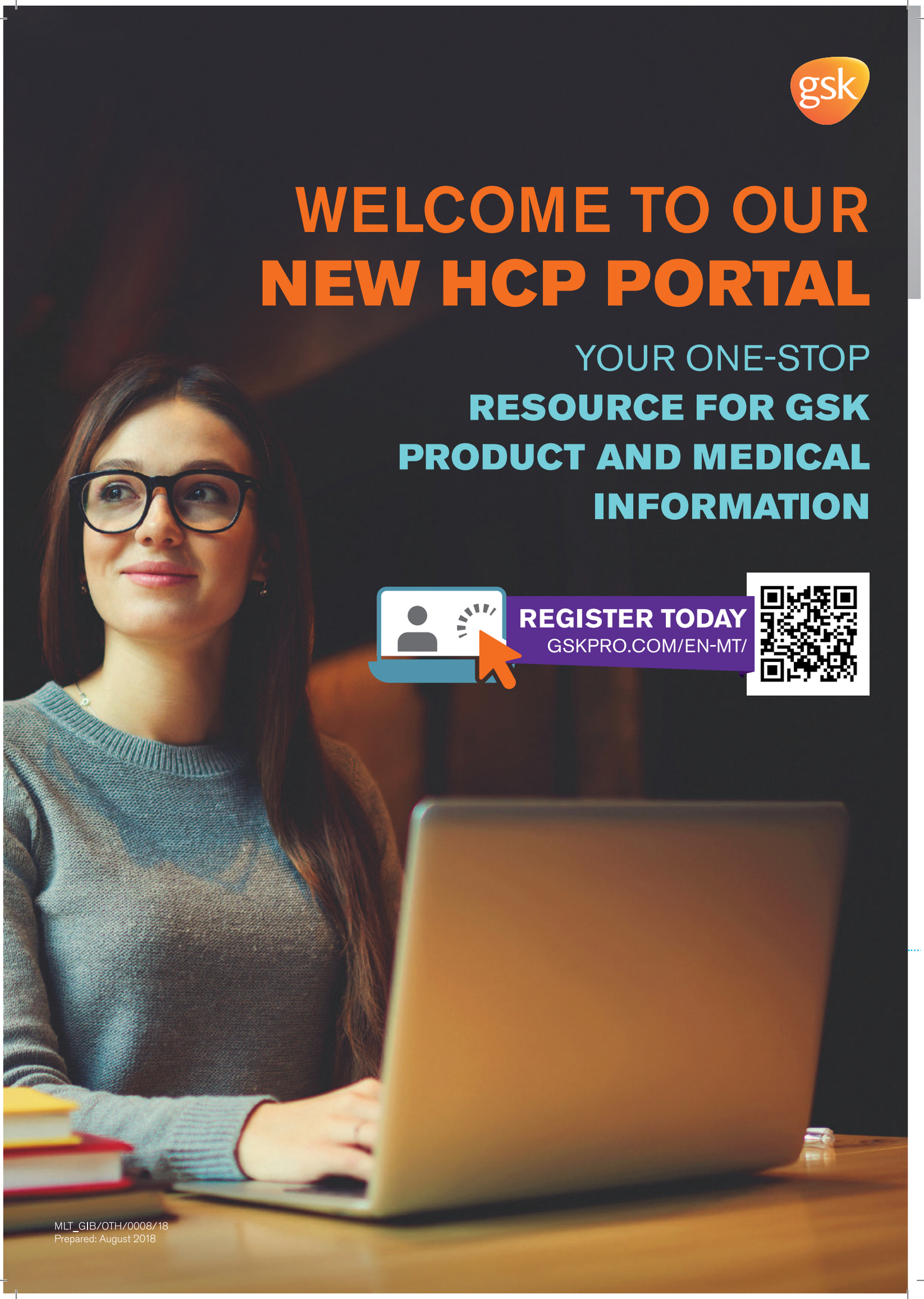
## New Developments in Breast Cancer Detection

## Migraine

## Embracing Depression: The Role of the Primary Care Physician

## Meeting Rev. Dr Raymond Portelli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EDITORIAL

# MOORFIELDS EYE HOSPITAL, AI & PARADIGM SHIFTS

The application of AI in medicine has always intrigued clinicians, so much so that Elsevier started publishing the journal *Artificial Intelligence in Medicine* way back in 1989. To put you into perspective, this was a period where we experienced the initial years of marketing of fluoxetine & lovastatin [the first statin], as well as the fall of the Berlin Wall. Way back in 1989 *Artificial Intelligence in Medicine* discussed 'Machine over mind', "Deep' models and their relation to diagnosis', 'Expert systems in laboratory medicine and pathology' and the likes.

Here we are, merely 30 years later, championing a machine which can learn to interpret eye scans with an error rate of only 5.5%! Indeed, in the study conducted by Moorfields Eye Hospital NHS foundation trust, the University College London and Google's DeepMind Technologies Limited, published in the journal *Nature Medicine*,[1] the authors found that the said machine can learn to read complex eye scans and accurately detect more than 50 eye conditions. To put it simply, the London-based DeepMind created an algorithm enabling a computer to analyse optical coherence tomography (OCT), a high resolution 3D scan of the retina. Approximately 15,000 anonymized scans were used to 'train' the machine how to read OCTs. The next step involved the ultimate challenge of the machine against mankind … the AI & eight clinicians were asked to triage 1,000 patients whose clinical outcomes were already known. AI performed as well as leading retina specialists, with an error rate of 5.5%. Of significance is the fact that the algorithm did not miss a single urgent case.

Although all this seems really exciting, a question naturally comes to mind … what's the next step? Well, seeing the AI system through the clinical trial phase and subsequent regulatory approval; if granted approval, the system will then be available for use across all of Moorfields' sites. Currently DeepMind is also doing research with Imperial College London to improve the accuracy of breast cancer screening, as well as University College London Hospitals to examine whether AI can differentiate between cancerous and healthy tissue on scans.

Needless to say, the speed in diagnosis and the simultaneous reduction in diagnostic errors makes AI a most needed prioritisation tool. Things as they are, AI also has a scope in the training of clinicians. However, AI certainly raises a number of ethical and societal questions which need to be addressed including validation of AI systems, who is ultimately responsible when AI is used to support decision-making, mechanisms of ensuring the security and privacy of potentially sensitive data, to name a few. This has been clearly laid out by the Nuffield Council on Bioethics.

Once again, it seems apt to end this editorial with Nicholson Price's note in his piece *Black Box Medicine*, namely that medicine "already does and increasingly will use the combination of large-scale high-quality datasets with sophisticated predictive algorithms to identify and use implicit, complex connections between multiple patient characteristics."[2]
Quo Vadis?


REFERENCES

1. De Fauw J, Ledsam JR, Romera-Paredes B, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nature Medicine* 2018. Published 13 August 2018 [online]. Available from: http://www.nature.com/articles/s41591-018-0107-6
2. Price N. Black-Box Medicine. *Harv. J.L. & Tech* 2015;28(2):420-467.



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## Put depression behind them.

References: 1. Nutt DJ, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, *et al.* The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. J Psychopharmacol 2007; 21: 461–471.

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## ISSUE GUIDE



TheSynapse

# MIGRAINE

DR NAOMI PISCOPO
& DR MARIA CAUCHI

## ABSTRACT

Migraine is a very common neurological disorder affecting people from numerous age groups and it has been a subject for ongoing research over the past years. Studies have described vascular and neurological pathways as well as cortical spreading depression as being the underlying mechanisms responsible for the symptomatology of the disorder. Multiple triggers have been implicated, out of which genetic susceptibility is very significant. The varied clinical picture of migraine has led to the development of various forms of management ranging from non-specific to very specific preventive, acute and chronic treatment.

**Keywords:** Vascular and Neurological Mechanisms, Cortical Spreading Depression, Genes, Migraine Management

## INTRODUCTION

Migraine is classified as a primary headache disorder which manifests as recurrent painful headache attacks. These attacks differ in frequency amongst individuals and also in duration ranging from an hour up to even three days. The prevalence is higher in females (18%) than in males (6%).[1] Generally, the onset of migraine is seen at around puberty, with the onset of menarche in females, with its effects peaking between the ages of 35 and 45 and declining thereafter.[2]

## PATHOPHYSIOLOGY

The pathophysiology of migraines is best described through an interaction of vascular and neurogenic theories hence making the disorder of neurovascular origin. Thomas Willis described how the pain experienced from the headache is a result of vasodilation of the meningeal and cerebral arteries.[3] It was later established that there is an interaction between the brain's neural activity and the mentioned blood vessels. Migraine is known to be associated with hypertension, stroke, and a patent foramen ovale, hence confirming the role of the vascular system in its pathophysiology.[4]

In 2013, Amin et al conducted imaging studies during spontaneous migraine attacks and concluded that the dilation of blood vessels is not the principal cause of central and peripheral pain.[5] It is the proinflammatory agents as well as neuropeptides released from trigeminal nerve afferents within the meninges that trigger the pain. This occurs together with the vasodilation via sensitization of both the central and peripheral neurons in the trigeminovascular system.[6] Genetic variability is an important component that influences the susceptibility of developing this problem, as well as the severity of the symptoms.[7]

The trigeminal nerve and its fibres innervate a set of intra- an extra- meningeal blood vessels and this is what makes up the trigmeninovascular system.[8] Nerve endings from this system innervate both intracranial and extracranial structures such as venous sinuses and the eye respectively. During the pain phase of the condition the trigeminovascular system is activated and initiates a cascade of events from the sensory nerve endings of the trigeminal nerve. Vasoactive neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide, neurokinin A and nitric oxide are usually stored in the trigeminal nerves.[9] When released, they lead to vasodilation and increased blood flow which result in oedema in the meningeal vascular system further worsening the sensation of pain as demonstrated in Figure 1.[10] Furthermore, upon stimulation of the trigeminal nerve system, structural changes of the dura mater have been noted including mast cell degranulation as well as changes in the postcapillary venules such as platelet aggregation.[11]

Another important phenomenon is linked to migraine aura; the cortical spreading depression (CSD) was first described in 1943 by a Brazilian neurophysiologist.[12] This is an electrophysiological event described as an intense wave of neurological activity within the brain at a rate of 2-5mm/min which slowly spreads over cortical brain regions and precedes a prolonged period of depressed neural activity as it interferes with calcium, potassium and sodium ion gradients.[13] It has been

proven that CSD activates the trigeminovascular system hence contributing to the pain.[14] CSD is implicated in visual aura where the visual field is affected, starting at the centre and spreading to the periphery at a rate of 3mm/min.[15]

## AETIOLOGY

Migraine has a strong genetic component, also stemming from the interaction which multiple genes - particularly those concerned with neural, vascular, hormonal and mitochondrial systems - have with environmental factors.[7] Genes coding for serotonin and dopamine systems have been studied and an association has been identified between the human serotonin transporter SLC6A4 gene and migraine. The latter gene codes for a membrane protein that removes serotonin from the synapse and recycles it back into neurons.[16] During a migraine attack, serotonin levels are known to be decreased and this leads to neuropeptide release. Dopamine's interaction with its receptors in the trigeminovascular system is implicated in the prodromal symptoms experienced.[17] A range of food items have been identified as triggering factors and include chocolate, alcohol, cheese and dairy products.[18] The fact that migraine attacks are more common in women post-puberty may be explained by the fluctuating levels of female hormones during the menstrual cycle which interact with oestrogen and progesterone receptors, rendering females more susceptible. Both during pregnancy and post-menopause, hormonal levels are relatively constant and it is during these times that migraine episodes decrease.[19] Other known triggering factors include exercise, the oral contraceptive pill and variations in the sleep-wake cycle.

## SYMPTOMS AND SIGNS

The typical presentation of migraines is of a severe unilateral headache which may be pulsatile. Nausea, vomiting and photophobia are commonly associated features.[20] There may also be allodynia, lacrimation, ptosis, depression and transient amnesia.[21] Before a patient experiences the headache, there may be a prodrome and an aura which arise from areas in the cortex, brainstem, hypothalamus and limbic system. The prodromal phase consists of symptoms which precede the headache by several hours and include food cravings, irritability, and fatigue.[20] The migraine aura is a separate phase of a migraine attack consisting of focal neurological symptoms which last from five minutes till one hour before migraine headache onset and then resolves completely. Symptoms and signs may be positive or negative indicating gain-of-function or loss-of-function respectively. Examples include tremor or muscle weakness if the motor cortex is affected or flashing lights and scotomas when the somatosensory cortex is involved. Aphasia will result if the speech area is affected.[22]

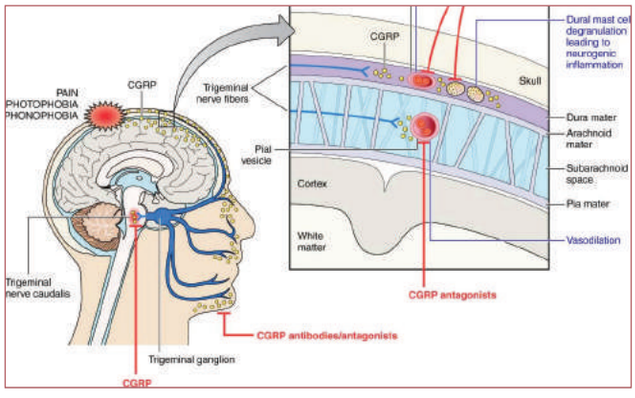


**Figure 1.** During a migraine attack CGRP is released from trigeminal nerve afferent fibres both centrally and peripherally. This leads to inflammation and vessel dilation. CGRP antibodies block or reduce CGRP levels peripherally whilst CGRP antagonists act centrally to suppress the effects of CGRP.

**Source:** Russell FA et al. Calcitonin Gene-Related Peptide: Physiology and Pathophysiology.[10]

## MANAGEMENT

The non-pharmacological management of migraine includes reassessment of the patient's diet and lifestyle. Therapy sessions including relaxation and cognitive behavioural therapy have also been proven useful.[23] NSAIDs and other simple analgesics, such as paracetamol, together with the anti-emetic metoclopramide may also be used during an acute migraine episode.[24] The more specific anti-migraine drugs include ergot and triptan derivatives which demonstrate agonistic properties on serotonin receptors and are also used in the acute phase. Locally, Zolmitriptan is the triptan mostly in use. The release of neurotransmitters from central and peripheral trigeminal nociceptive nerve terminals can be inhibited by the serotonin-5HT1B/1D receptor agonist zolmitriptan as well as ergot alkaloids, and indomethacin.[25] Triptans exert their effect by causing intracranial vasoconstriction and also reduce neuropeptide extravasation.[23] Studies have proved the benefit of using combinations of NSAIDs and triptans to improve outcome.[26] Although the majority of patients do not require preventive medication, this should be considered if the patient's quality of life is significantly affected, if there are frequent attacks and in case of unresponsiveness to acute treatment. Amongst the most effective and preventive drugs in use is the beta-blocker propranolol which has been showed to reduce migraine frequency by more than 50%. Tricyclic antidepressants particularly amitriptyline, calcium channel blockers including verapamil and flunarizine as well as anti-epileptic medications such as carbamazepine, gabapentin, valproic acid and topiramate are also used.[27] Modern treatment under development entails the use of humanized monoclonal antibodies against CGRP and its receptors which are implicated in the pathophysiology of migraine.[28] More complex targeted therapy for migraine is brain modification; transcranial magnetic stimulation is one example where brain excitability is modified.[29]

## CONCLUSION

Migraine episodes have consequences on the patient's quality of life as it may interfere with employment, their capability to take care of their families and social relationships. This may be measured using the Migraine Disability Assessment where higher scores are associated with greater levels of disability.[30] Given the complexity of the condition, research and studies are on the increase so as to gather more knowledge and hence be able to understand and manage this debilitating disease better.

REFERENCES CAN BE ACCESSED ON THESYNAPSE.NET

# NEW DEVELOPMENTS IN BREAST CANCER DETECTION

DR PIERRE VASSALLO

Imaging options for breast cancer detection have changed significantly over time. There are two goals that drive technological change in breast cancer imaging: a. improvement in diagnostic accuracy and b. reduction in radiation exposure to the breast.

The gold standard for breast cancer detection has long been the standard two-plane mammogram; this was initially obtained using conventional film/screen technology and later with full field digital mammography (FFDM), which improved image quality and reduced radiation exposure.

Digital breast tomosynthesis (DBT) integrates tomography into digital mammographic technology. This imaging method obtains multiple slices through the thickness of the breast thereby reducing interference from tissue overlap, which is particularly advantageous in dense breasts. The current practice is to start with FFDM as the initial screening test and to proceed to DBT only if questionable findings are noted on FFDM.

From a cancer detection standpoint, combining FFDM and DBT improves cancer detection rates (CDR), however this also leads to doubling in radiation dose delivered to the breast. Performing DBT alone is not recommended as it involves longer reading times and does not deliver the initial overview of the breasts provided by FFDM, which greatly aids cancer detection.

Recent technological development in DBT has led to synthesised views (or S-views), which are single mammographic images created from the DBT data. An S-view image is similar to an FFDM mammogram. Using DBT/S-views reduces the radiation dose by 50% compared with FFDM/DBT combined. DBT with S-views may therefore be used as a primary cancer screening exam to replace FFDM/DBT.

Current scientific literature analysing over 30,000 screening exams has shown an improved CDR with DBT/S-views (9.3 per 1000 screening exams) compared with FFDM (5.4 per 1000 screening exams); the relative (detection) rate (RR) is 1.72. Using DBT/S-view improves CDR irrespective of breast density, but the benefit is greater for dense breasts; RR for is 2.86 for high density breasts and 1.52 for low density breasts. The positive predictive value (PPV), which is the proportion of correct positive diagnoses, using DBT/S-view (23.3%) is double that of FFDM (12.9%).[1]

An important criterion for assessing a screening test is the recall rate; since mammograms are taken in the absence of a radiologist in most screening programs, patients need to be recalled for further investigation if the radiologist detects an abnormality. A very high recall rate is associated with significant

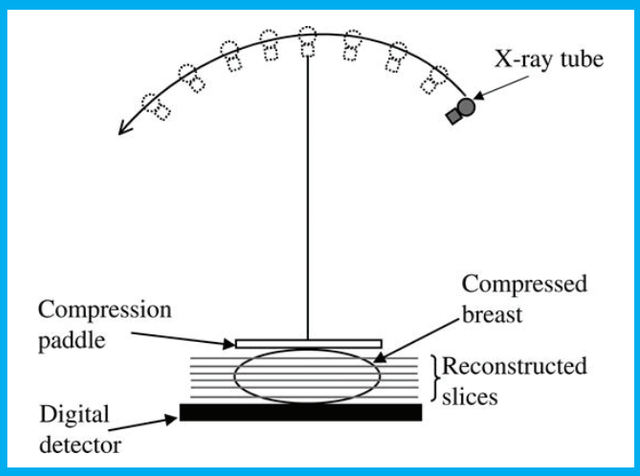


**Figure 1:** Diagram showing movement of X-ray source to obtain slice images through the breast.

distress and expense, since many of the recalled patients will not have cancer. A low recall rate, however, may miss cancers. The recall rate for DBT/S-view is similar to FFDM.

The review time required by the radiologist for DBT/S-view is however almost double that of FFDM.

Similar results were obtained in earlier studies from different research groups;[2] they described significant reduction in radiation dose using DBT/S-view technology compared with DBT/FFDM combination.

Tomography uses a long-known principle that acquires a slice image through the body by moving the X-ray source and detector during the image acquisition (Figure 1). This movement retains in focus those structures that are at the focal point of rotation, while blurring all structure in front of and behind that plane of focus. The use of tomography started in the 1930s and was enhanced in the late 1960s and 1970s with the development of powerful computers that could handle large volumes of data fast. These technologies gave rise to Computed Tomography (CT), which is one of our most powerful diagnostic tools.

Integration of tomography into breast imaging was suggested in the late 1990s, however prototype systems that were developed were not practical due to limited detector technology and computing power. With the improvement of x-ray detectors and computing power, DBT systems have been increasingly introduced into clinical use over the past decade (Figure 2).

**Figure 2:** Clinical implementation of DBT

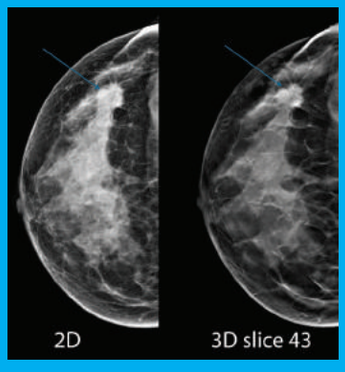


**Figure 3:** FFDM (Left) and DBT (Right) showing a cancer (arrows) in the lateral aspect of the left breast

DBT has been used to evaluate complex and equivocal findings as part of a diagnostic mammographic imaging work-up (Figures 3 and 4), but its implementation for breast cancer screening was hindered due to increased radiation exposure it entails.

By employing the latest development in DBT, namely the S-view, the radiation exposure is reduced to by half, which makes it acceptable for use in breast cancer screening. The diagnostic accuracy of the DBT/S-view is higher than that of the standard FFDM/DBT combination (Figure 5) according to the latest research.[1]

Breast cancer is the most common cancer in women account for around 50% of all female cancers. The frequency of breast cancer and the availability effective treatment

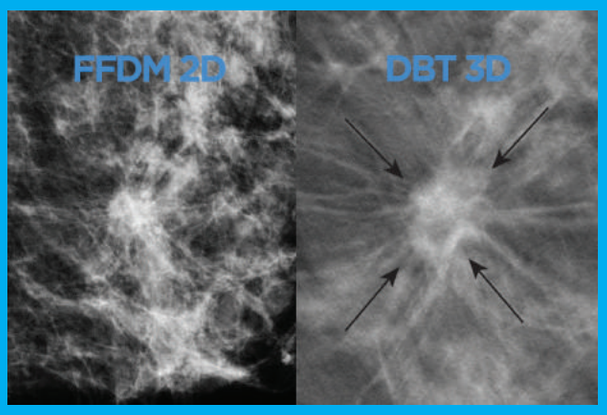


**Figure 4:** Zoomed image of a cancer (arrows) in a dense breast seen on FFDM (Left) and DBT (Right)

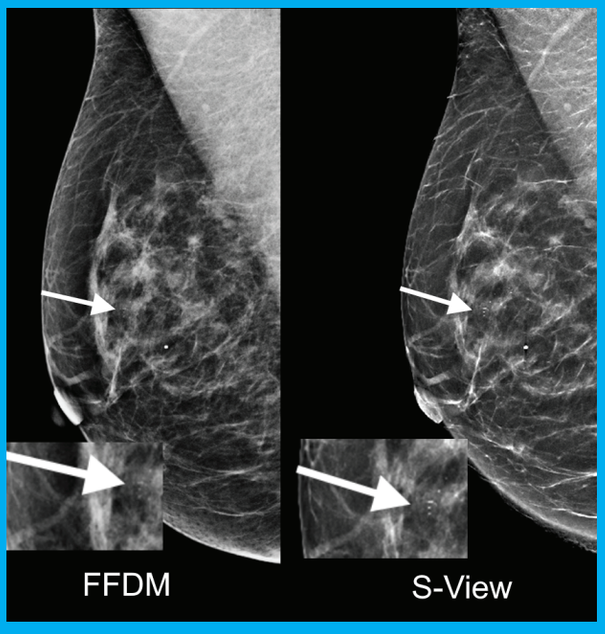


**Figure 5:** FFDM (Left) and S-view Mammogram (Right) of the same breast; microcalcifications (arrows) are shown more clearly on the S-view that on the FFDM (note zoomed inserts)

justify regular screening for **all** women particularly those who have risk factors. The dense breast is one of the limitations of mammographic imaging and is also a risk factor for breast cancer. The S-view technology provides a more accurate and safe method of screening for breast cancer than was previously possible. This is particularly true when evaluating dense breasts.

REFERENCES

1. Caumo F, Zorzi M, Brunelli S, et al. Digital Breast Tomosynthesis with Synthesized Two-Dimensional Images versus Full-Field Digital Mammography for Population Screening: Outcomes from the Verona Screening Program. Radiology 2018;287(1):37-46.
2. Aujero MP, Gavenonis SC, Benjamin R, et al. Clinical Performance of Synthesized Two-dimensional Mammography Combined with Tomosynthesis in a Large Screening Population. Radiology 2017;283(1): 70-76.

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Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions:** Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. **Angioedema:** Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. **Interactions:** Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be coadministered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. **Fertility, pregnancy and lactation:** The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. **Undesirable effects:** Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. **Packs sizes:** Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. **Legal classification:** POM. Marketing **Authorisation Holder:** Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **Marketing Authorisation Numbers:** Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. **Please refer to the Summary of Product Characteristics (SmPC) before prescribing.** Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222572. 2018-MT-ENT-30-APR-2018

**References: 1.** Fala L. Entresto (sacubitril/valsartan): first-in-class angiotensin receptor neprilysin inhibitor FDA approved for patients with heart failure. *Am Health Drug Benefits*. 2015;8(6):330-334. **2.** Volpe M, Camovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci*. 2016;130(2): 57-77. **3.** Ponikowski P, Voors A, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37(27):2129-2200. **4.** Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017; 136(6):e137-e161. Epub 2017 Apr 26" **5.** ENTRESTO Core Data Sheet, version 1.1. Novartis Pharmaceuticals, August 2015. **6.** McMurray JJV, Packer M, Desai AS, et al. Dual Angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure. *Eur J Heart Fail*. 2013;15(9):1062-1073. **7.** McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.

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EDITOR'S PICK
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# A CAMEO MENTION OF GAMMA-GLUTAMYLTRANSFERASE (GGT)

DR MICHELLE MUSCAT

## A MAGICAL GARMENT GIRL USING ALCOHOL TO BREAK A SPELL

### MANGA & LIGHT NOVEL

**Title:** Kore wa Zombie Desu ka? of the Dead
**Author:** Shinichi Kimura (light novel & manga)
**Illustrations Light Novel:** Kobuichi & Muririn
**Illustrations Manga:** Sacchi
**Publisher:** Fujimi Shobo

### ANIME TV SERIES

**Director:** Takaomi Kanasaki
**Writer:** Makoto Uezu
**Run:** 2011-2012


In a conjectural universe where a boy is resurrected as a zombie by a necromancer, and a young girl is cursed to assume the semblance of a middle-aged man, being able to revert to her original self when drunk, it is interesting, somewhat unexpected and refreshing to hear the said character specifically, very briefly, voice concern that her gamma-glutamyltransferase (GGT) levels were abnormally high.

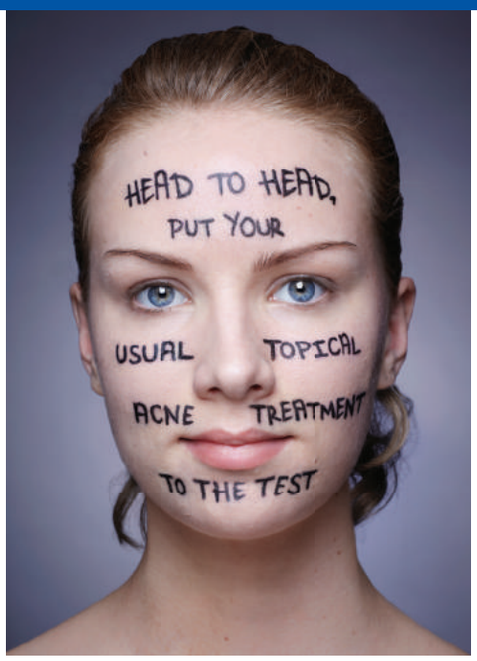
In this hypothetical universe, the most absurd things can happen… including a boy transforming into a magical zombie girl, with two other protagonists being a necromancer and a vampire ninja… In such a show where comedy reigns supreme, one remains amusingly surprised when a young girl, who temporarily takes the semblance of an older man, complains specifically that in that form her GGT and cholesterol levels were elevated. In "Kore wa Zombie Desu ka?" (written by Shinichi Kimura and adapted to anime by Studio Deen), the girl in question was constantly seen to be drinking alcoholic beverages, which were somehow related to breaking the spell that made her assume the body of a middle-aged man. GGT is mentioned briefly, in a somewhat 'cameo appearance' style in episode 7 of the second series, "Kore wa Zombie Desu ka? Of the dead". It is worthy of note that this line was modified in the English adaptation to reflect terminology more well known to the general public, namely making reference to enlargement of the prostate with advancing age.

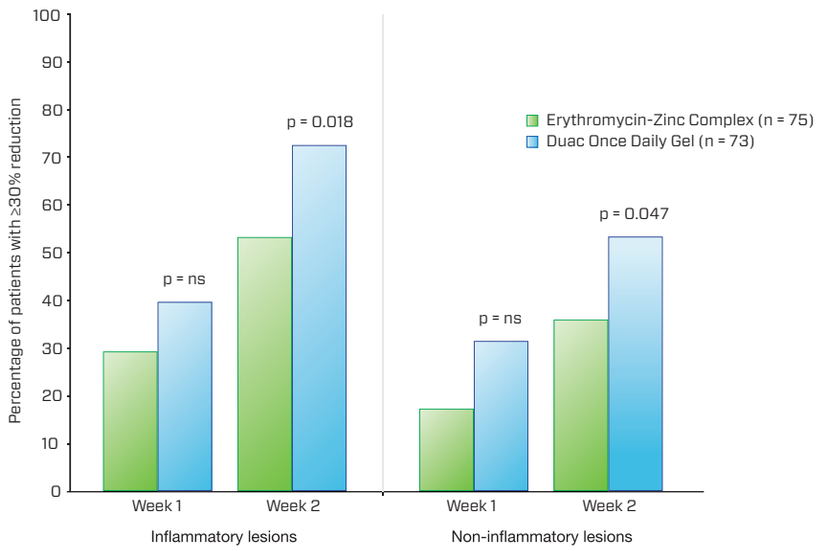

GGT is indeed one of the traditional and well known biochemical indicators of alcohol abuse, however lacks high specificity for this purpose. Some other biochemical markers of alcohol consumption include carbohydrate-deficient transferrin (CDT), phosphatidylethanol (PEth), and urine ethyl glucuronide (EtG) and ethysulfate (EtS).[1-8] The ratio of serum aspartate aminotransferase to alanine aminotransferase (AST/ALT ratio) is also used as a potential indicator of alcoholic liver disease.[9,10]


REFERENCES

1. Geppert B, Tezyk A, Zaba C. [Biochemical markers for acute and chronic alcohol consumption]. Przegl Lek. 2012;69(10):1163-7.
2. Das SK, Nayak P, Vasudevan DM. Biochemical markers for alcohol consumption. Indian J Clin Biochem. 2003;18(2):111-8.
3. Sharpe PC, McBride R, Archbold GP. Biochemical markers of alcohol abuse. QJM. 1996;89(2):137-44.
4. Rosman AS. Utility and evaluation of biochemical markers of alcohol consumption. J Subst Abuse. 1992;4(3):277-97.
5. McDonell MG, Skalisky J, Leickly E, McPherson S, Battalio S, Nepom JR, et al. Using ethyl glucuronide in urine to detect light and heavy drinking in alcohol dependent outpatients. Drug Alcohol Depend. 2015;157:184-7.
6. Anton RF. Commentary on: ethyl glucuronide and ethyl sulfate assays in clinical trials, interpretation, and limitations: results of a dose ranging alcohol challenge study and 2 clinical trials. Alcohol Clin Exp Res. 2014;38(7):1826-8.
7. Schrock A, Hernandez Redondo A, Martin Fabritius M, Konig S, Weinmann W. Phosphatidylethanol (PEth) in blood samples from "driving under the influence" cases as indicator for prolonged excessive alcohol consumption. Int J Legal Med. 2015.
8. Walther L, de Bejczy A, Lof E, Hansson T, Andersson A, Guterstam J, et al. Phosphatidylethanol is Superior to Carbohydrate-Deficient Transferrin and gamma-Glutamyltransferase as an Alcohol Marker and is a Reliable Estimate of Alcohol Consumption Level. Alcohol Clin Exp Res. 2015;39(11):2200-8.
9. Gurung RB, Purbe B, Gyawali P, Risal P. The ratio of aspartate aminotransferase to alanine aminotransferase (AST/ALT): the correlation of value with underlying severity of alcoholic liver disease. Kathmandu Univ Med J (KUMJ). 2013;11(43):233-6.
10. Nyblom H, Berggren U, Balldin J, Olsson R. High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol Alcohol. 2004;39(4):336-9.

# HEAD TO HEAD, DUAC WORKS FASTER THAN ERYTHROMYCIN-ZINC COMPLEX[1]




Graphs adapted from Langner A *et al.* JEADV 2007

- More patients with mild to moderate acne achieved at least a 30% reduction in inflammatory and non-inflammatory lesion counts at week 2 with Duac than Erythromycin-zinc complex[1]
- DUAC demonstrated a faster onset of action, reducing total lesion count in significantly more patients than Erythromycin-zinc complex at just 2 weeks[1]
- Most common side effects include erythema, peeling, dryness, burning sensation, photosensitivity and headache

## DUAC INDICATIONS & USAGE ADVICE[2]

- Duac Once Daily Gel is indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above[2]
- Formulation contains added moisturisers, glycerin and dimethicone, for better tolerability[4]


## YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE

Duac comes ready-mixed, and is easy for your patients to use. It is recommended that you offer the following guidance[3]: Once-daily, in the evening, your patients should[2]:

• Thoroughly wash the affected area of skin

• Gently pat dry

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

**TIPS[3]**

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

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

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

**TRADE NAME:** Duac Once Daily Gel 10mg/g + 50mg/g. **ACTIVE INGREDIENTS:** Clindamycin phosphate/anhydrous benzoyl peroxide. **PHARMACEUTICAL FORM:** Gel. **INDICATIONS:** Topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions in adults and adolescents from 12 years of age and above. **POSOLOGY:** *Adults and Adolescents (12 years and over):* Once daily (evening) to affected area. Should not exceed more than 12 weeks. Applied in a thin film after washing gently with mild cleanser and fully drying. Was hands after application. **CONTRAINDICATIONS:** Hypersensitivity to active substances/lincomycin/excipients. **PRECAUTIONS:** Avoid Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated/broken skin. Caution in patients with a history of regional enteritis, ulcerative colitis, antibiotic-associated colitis, atopic patients, concomitant topical acne therapy. Increase in peeling and reddening will occur in most patients during first few weeks of treatment. If severe local irritancy, discontinue. Prolonged exposure to sun should be avoided. In patients with sunburn, this should be resolved before use. If significant diarrhoea/abdominal cramps occur, discontinue (symptoms may indicate antibiotic-associated colitis). May bleach hair or coloured fabrics. Patients with a recent history of systemic or topical clindaymcin and erythromycin are more likely to have pre-existing anti-microbial resistant *Propionibacterium acnes* and commmensal flora. Cross-resistance: May occur when using antibiotic monotherapy. **PREGNANCY/FERTILITY /LACTATION:** *Pregnancy:* only after careful risk/benefit assessment. *Fertility:* no data. *Lactation*: should not be applied to breast area. **UNDESIRABLE EFFECTS:** *Very common (≥1/10)*: erythema, peeling, dryness. *Common (≥1/100 & <1/10)*: burning sensation. *Refer to the SPC for full list of undesirable effects.* **LOCAL PRESENTATION:** 30g gel. **MARKETING AUTHORISATION NUMBER:** MA300/01401. **MARKETING AUTHORISATION HOLDER:** GlaxoSmithKline UK Ltd. **Legal Category:** POM. **Date of Preparation:** September 2017.



***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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**References: 1.** Langner A *et al.* JEADV 2007; **21**: 311-319. **2.** Duac 5% Summary of Product Characteristics, January 2015. **3.** Duac 5% Patient Information Leaflet, October 2014. **4.** Langner A *et al.* BJD 2008; **158**: 122-129

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For more information
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Duac once daily gel — *Clindamycin 1% and benzoyl peroxide 5%*

Job no.: MLT_GIB/CBP/0002/17 Date of preparation: November 2017

# EMBRACING DEPRESSION

DR AMY CHRISTINE CHIRCOP

## THE ROLE OF THE PRIMARY CARE PHYSICIAN

Although perceptions of mental illness have changed for the better over the past years, for reasons unbeknownst, mental health issues remain a lingering taboo. This has led to many mental illness sufferers feeling side-lined, isolated, ashamed and worthless; fearing being labelled as a liability or "mental". This can pull the final trigger for those teetering on the mental health ledge. After all, our brain is another part of our body - so why shouldn't we talk freely about it, just like we would talk about a broken bone?

This article aims to explore the role of the primary care physician in the management of such an important health aspect.

### WHAT ARE THE NUMBERS?

According to the World Health Organisation (WHO), mental disorders are the greatest contributors to chronic conditions affecting the European population. Depression tops the list - it accounts for 11% of all 'years lived with disability' (YLDs), making it the leading chronic condition in Europe. Anxiety disorders account for 4% of YLDs.[1] Rates for mood disorders in women are significantly higher when compared to men (33.2% vs. 21.7%).

WHO highlight the contributing role of GPs as follows:

- 74% of countries report that GPs identify and refer people with severe and enduring mental health problems
- 52% report that GPs diagnose such disorders
- 40% report that GPs also give treatment.[2]

### MANAGING DEPRESSIVE DISORDER IN PRIMARY CARE

General practitioners provide a "person-centred, continuing, comprehensive, and coordinated whole-person health care to individuals and families in their communities".[3] Given that GPs tend to know their patients and families on a more personal level, patients might feel more comfortable to open up with their GP about any problems encountered. Physicians might fall into the trap of inquiring only about physical symptoms and attempt to treating them; without exploring whether there are any causes to these symptoms apart from somatic ones, such as mood disorders, resulting in depression going undiagnosed. A study by Simon et al.[4] showed that 69% of patients diagnosed with major depressive disorder presented to primary care solely with physical symptoms. These might include chest pain, joint pain, limb pain, back pain, gastrointestinal symptoms, fatigue, psychomotor activity changes and appetite changes.

In 2015 Strakowski and Nelson[5] came up with a seven-key component strategy which can be employed in the primary care setting when managing a patient with depression:

#### *Comprehensive assessment*

Several validated and effective screening tools have been developed in order to identify and measure the severity of depressive symptoms; a popular choice being the nine-item Patient Health Questionnaire (PHQ-9).[6] This questionnaire may be filled out by the practitioner or the patient himself, and is not only used in the initial stages of management, but also as an effective tool in assessing response to management. It addresses whether each of the nine DSM-IV criteria for depression such as anhedonia, poor appetite and thoughts of self-harm were present over the two weeks prior to the compilation of the questionnaire and scores each criterion from 0 to 3; 0 meaning that the features were not present, whilst a score of 3 indicates that the features were present nearly every day. A total score of less than 10 might indicate that conservative treatment should be applied such as counselling, relaxation strategies and exercise; on the other hand, a score greater than 19 indicate severe depression and medical treatment should be employed.[7]

#### *Ongoing safety evaluation*

During this stage, suicide risk should be addressed. It is vital to identify any potential risk factors and protective factors. Patients tend to avoid bringing up this subject unless asked directly. The highest predictor of self-harm or suicide is a previous attempt. Protective factors include a good support system such as family, and in certain cases, religion. Furthermore, alcohol and drug use should be enquired about since these may be resorted to by patients passing through a difficult period in their life, and they are depressogenic in themselves, resulting in the patients spiralling into a hazardous vicious cycle.

### *Setting treatment goals*

Setting realistic treatment goals is crucial, whilst adopting a biopsychosocial approach; and this should be done hand in hand with the patient together with family or other supportive figures. The fears and concerns of the patient should be explored and any potential stressors exacerbating the situation should be identified. Furthermore one should explore what the individual wants to achieve, since this will also direct what type of treatment is chosen.

### *Agreed upon treatment plan to meet goals*

NICE recommends that the management of depression should be in a stepped care approach, that is, the least burdensome treatment which achieves effect, even if it is just watchful waiting, should be employed. Furthermore, it reports that a significant proportion of patients recover without any medical interventions.[8] In mild to moderate depression, one may opt to resort to conservative measures such as sleep hygiene and active monitoring, or else step up to psychological therapy, one form of which is cognitive behavioural therapy (CBT). CBT, pioneered by Ellis[9] and Beck[10] in 1962 and 1970, respectively, refers to interventions that aim to change maladaptive cognitions leading to a reduction in emotional distress and problematic behaviour. In cases of more severe symptoms, anti-depressant treatment is recommended; 1st line treatment recommended by NICE is SSRIs.[8] Medications may be employed in conjunction with psychological interventions. It is of vital importance to discuss that these medications take three to four weeks for the full effect to be exerted and potential treatment side-effects should be mentioned. In severe cases, or where suicide risk is high, referral to specialist care or services should be sought promptly.

### *Good support network*

Fighting depression is no easy task; patients may often succumb to their feelings of hopelessness and helplessness, and both medications and behavioural interventions take a fair deal of time for their effects to be evident. It is therefore important to support these patients through frequent follow-up visits, which can eventually be spaced out if the patients are responding well to treatment or interventions. Apart from ensuring that patients have a good support network from friends and families, they can also be referred to special entities and organisations.

### *Mood monitoring*

As part of the management of depressive disorder, Dr. Strakowski[5] suggests the use of mood charting where patients record their mood and depressive symptoms on a daily basis. Apart from involving the patients actively in his own management, patients would have a graphical representation of how they are responding to treatment. Furthermore, it can guide the physician in terms of treatment, since when asked how they are doing, "patients tend to report how they have been feeling over a period of time based on how they are feeling at that specific moment", which can be misleading.

### *Create meaningful appointments*

As already mentioned, organising regular follow-up appointments is of vital importance. Through these appointments, mood charting may be monitored and reviewed, suicidal risk re-assessed, and compliance to treatment ensured. Drug and alcohol use should always be enquired about. Another important issue is treatment side-effects especially those related to sexual dysfunction, a common side-effect with SSRIs which patients might be hesitant to report. What is more is that general health measures should always be supported; these include a good balanced diet, exercise and sleep. In cases where patients do not seem to respond to treatment, then ideally specialist advice or referral should be sought.

## CONCLUSION

The pivotal role of the primary care physicians in relation to the management of several mental health disorders throughout our community remains, to this very day, undisputed. Physicians also have an important responsibility in assuring that what has, for a long stretch of time, been considered by many as a lingering taboo, will be shelved as something of the past; thus ascertaining that patients feel that they can enjoy the same level of treatment and support as for any other physical illness. Although remaining a recurring challenge, this paradigm shift now seems much more attainable than a few years back. The primary care physician must be looked at by patients as their pillar of strength, their very one individual upon whom they can rely on, no matter the circumstances. This will ensure that patients have enough trust in the former so much so that they feel safe confiding in them the daily challenges they face and consequently seek help.


REFERENCES

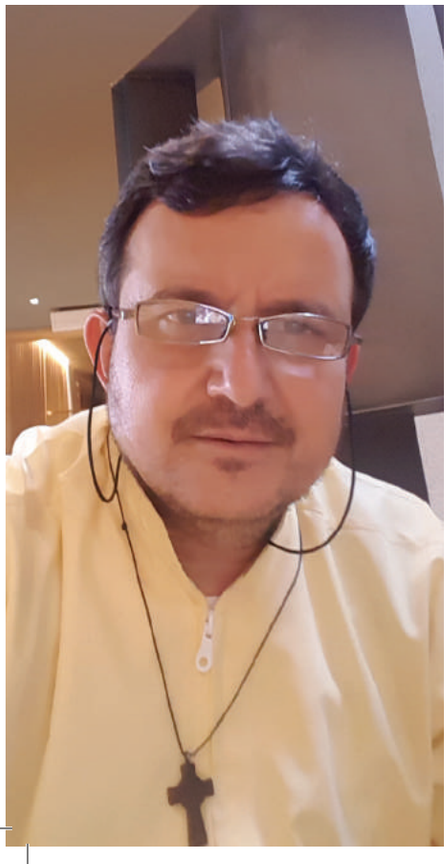
1. WHO. WHO methods and data sources for global burden of disease estimates 2000-2011. http://www.who.int/healthinfo/statistics/GlobalDALYmethods_2000_2011.pdf?ua=1. 2013. Accessed 28 May 2018.
2. WHO. Mental Health: Data and Resources. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/data-and-statistics. Accessed 28 May 2018.
3. RACGP. What is General Practice? https://www.racgp.org.au/becomingagp/what-is-a-gp/what-is-general-practice/. Accessed 28 May 2018.
4. Simon G, VonKorff M, Piccinelli M et al. An International Study of the Relation between Somatic Symptoms and Depression. New England Journal of Medicine 1999;341(18):1329-1335.
5. Strakowski S, Nelson E. Major depressive disorder (1st ed.). NY: Oxford University Press; 2015.
6. Kroenke K, Spitzer R, Williams J. The PHQ-9. Journal Of General Internal Medicine 2001;16(9):606-613.
7. Treating Depression and Anxiety in Primary Care. Prim Care Companion J Clin Psychiatry 2008;10(2):145-152.
8. The National Institute for Health and Care Excellence. Depression in Adults: Recognition and Management. Clinical Guideline 90. April 2018. https://www.nice.org.uk/guidance/cg90. Accessed 28 May 2018.
9. Ellis A. Some Omissions to Leonard Rorer's Review of Reason and Emotion in Psychotherapy. PsycCRITIQUES 2000;45(2): 234-235.
10. Beck A. Cognitive therapy: Nature and relation to behaviour therapy. Behaviour Therapy 1970;1(2):184-200.

MEETING PEOPLE

MARIKA AZZOPARDI MEETS REV. DR RAYMOND PORTELLI DURING A WHIRLWIND VISIT TO GOZO AND MALTA FROM HIS MISSION IN PERU

# A PRIEST & PRACTITIONER IN PERU

REVERAND DOCTOR RAYMOND PORTELLI



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### WHAT CAME FIRST, PRIESTHOOD OR MEDICINE?

I knew I wanted to become a doctor since my youth, while I was at Sixth Form. But during those years, I also felt the vocation to become a priest. I faced a dilemma. Should I become a doctor and a priest later, or vice versa? The then Bishop of Gozo, Monsignor Cauchi, insisted I should become a priest first and so, with due obedience, I began attending The Seminary in Gozo from where I was ordained a priest.

### DID YOU START MEDICAL STUDIES IMMEDIATELY AFTER?

No. I was sent to Peru as soon as I was ordained, spending 18 months in Lima and then moving to the small diocese of Iquitos deep in the Peruvian Amazon. However, once there, I learnt that the Amazonian National University was located close by and that it had its own Faculty of Medicine. So I spent the next eight years juggling my role as a parish priest with that of being a medical student. I finally graduated and obtained my licence in 2004.

### WHAT CHARACTERIZES YOUR TYPICAL DAY AT THE MISSION?

I do a mix of both professions. I work as a family doctor in a government clinic three times weekly. I also have my private practice (free to all who visit me) wherein I provide medical services to the poor and the needy. In the evening I don my cassock and carry out my clergyman's duties. Mass is celebrated in the evenings during weekdays and I am the only priest for a total of 18,000 inhabitants in the region.

### WHAT DOES YOUR WORK AS A MISSIONARY INVOLVE OTHER THAN THESE RESPONSIBILITIES?

I am responsible for four homes. One is named 'Something Beautiful for God' and is a home for Aids and HIV patients. Within its six rooms we have beds and a clinic. We felt this is a necessary service in this community, considering that Iquitos is the second city with the highest number of Aids sufferers in the country. We also run a small rehabilitation centre for drug addicts and a night shelter for the homeless where we can accommodate a maximum of 25 persons; these can also avail themselves of a free breakfast and showering facilities. Then there is also a small home for the elderly which retains 20 persons at a time.

### WHY IS THIS?

Liberal sex is rampant even though close to 80% of citizens are baptised Catholics. The poor bear the biggest brunt of the Aids scourge. Some do not possess an identification card. This means they are not entitled to any kind of treatment in the government clinics. So you get drug addicts for instance, with advanced Aids, sleeping rough and dying alone, untreated and uncared for. At our clinic we diagnose, treat and collaborate with the local hospital via our two doctors, together with a psychology team. Patients who make it to our clinic arrive in a bad state and many die within the week. This is mostly due to secondary infections, such as tuberculosis.

### HOW DO YOU CHOOSE YOUR PATIENTS?

We don't. They come to us. We never refuse patients, and keep them to sleep over within our facilities if their condition is bad enough. Otherwise they are treated as day patients.

> "SMALL MIRACLES HAPPEN DAILY"

### HOW DO YOU MANAGE ALL THIS?

Small daily miracles happen. But money is the most pressing need. We organise two big fund raisers a year in local parishes and the few middle class families usually give generous donations. This generally covers half the expenses we incur. The rest I manage to collect via fund raisers in Gozo.

### DOES YOUR WORK REQUIRE FREQUENT TRAVEL?

Once a month my team and I go out of Iquitos and visit the small communities of the river villages. The people there live simple lives in huts. But there are hundreds of villages and lots of people to treat.

### WHAT DO THE VILLAGERS SUFFER FROM TYPICALLY?

Respiratory diseases due to abrupt changes in temperature including bronchitis, pneumonia, diabetes, malaria, fungal infections, parasites, tuberculosis, etc. Unfortunately pneumonia kills a lot of children. Tuberculosis has become multi-drug resistant. I myself contracted it in 1996 but was cured. Still, I protect myself by setting limits in my relations with patients. People have poor education, namely due to the economic factor. We try our best to teach about the importance of cleanliness, hand washing and watching out for what one drinks.

### DO YOU HAVE ENOUGH HELP?

Well, as I explained earlier, I am the only priest in my parish. Recently a few groups of Maltese and Gozitans came to help with maintenance work, summer camps for kids, etc.

### WHAT MESSAGE WOULD YOU LIKE TO GIVE OTHER DOCTORS?

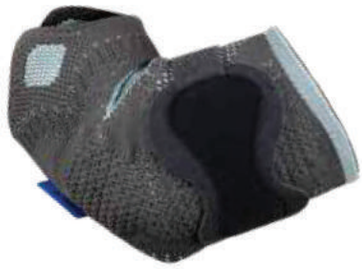
Don't forget the poor. Empathy is key. We must never put the humanistic aspect of our profession aside.

## I READ THE SYNAPSE BECAUSE...

The truth is that I have never read The Synapse, but I guess with this interview I will start reading it online. I hope it will be one way of keeping in touch with my fellow Maltese medical doctors.

# ELBOW BRACES AND TENNIS ELBOW ARMBRANDS

*Elbow braces*



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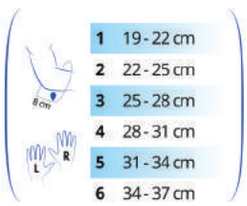


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| **1** | 19 - 22 cm |
| **2** | 22 - 25 cm |
| **3** | 25 - 28 cm |
| **4** | 28 - 31 cm |
| **5** | 31 - 34 cm |
| **6** | 34 - 37 cm |

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# LETTER TO THE EDITOR

**PROF. JOSEPH AZZOPARDI**
MD MRCP FRCP(L) FRCP(G) FRCP(E) FEFIM(Hon)
Specialist in Internal Medicine, Diabetes and Endocrinology

Dear Editors,

I write to correct certain distortions of the truth contained in your article entitled "The Medical Strike 1977-1987 Revisited" in issue 3 of TheSynapse that I received on the 7th August 2018.

If what you wrote in your article is simply a reflection of what the author wrote in his book, then you should have made this clear. If on the other hand you make what the author wrote your own, as you seem to do, then you should have checked your facts before you published the article.

You state that the strike stemmed from the inadequate salary structure of Government doctors. This is not true. In fact, the disagreement had nothing to do with money. The causes of the dispute were:

1. The power of the Medical Council to grant medical warrants; this ensured standards and objectivity in assessing qualifications to practice in Malta. In 1977 the Government legislated, transferring this power to the Minister of Health, enabling the latter to grant warrants without independent screening. The Medical Association objected to this.
2. A shortage of house physicians at that time. The Government had reacted to this by passing a law forcing newly qualified doctors to serve for two years in Government hospitals immediately after qualifying on pain of permanent professional exile. The Association wanted a more humane way of dealing with the matter.

False Government propaganda at the time tried to cloud the issue by giving the impression that the dispute was over a proposed health scheme. This was not the case. I know what the issues were. I was on the Medical Association of Malta Committee at the time.

In your article you state that the Medical Association organised a general medical strike; this again is not true. In response to the above laws the Association ordered a limited action that guaranteed emergency services. This action had the approval and support of the World Medical Association and the British Medical Association. Again, false Government propaganda tried to create the impression that the Medical Association had refused to provide for an emergency service.

Mintoff's Government savagely responded to the above limited trade union action by:

- Locking Government doctors obeying union directives out of state hospitals
- Barring these doctors from practising in private hospitals
- Dismissing these doctors from Government service with loss of pension rights

Not being able to make a living in Malta, the majority of Association doctors were effectively exiled, some never coming back. Many died abroad.

On the dismissal of Maltese doctors a number of foreign doctors were given a warrant by the Minister of Health to work in Malta. Many of these were not properly qualified. It was through the influx of these foreign mercenaries and the 'forty-five brand of brothers' you refer to in your article that the Government was able to lock out and dismiss specialists and doctors obeying their union. The result was a complete fracas of the medical service, with many patients paying with their health, some even with their lives.

As many of the dismissed Maltese doctors were University teachers, the local medical degree lost its international recognition. All qualifying doctors at the time were thus forced to remain working in Malta, thus 'solving' the above house physician issue. Many of the medical students went to finish their studies abroad, most never returning back

The dispute was a trade union matter and had nothing to do with politics, as the author of the book implies. Any civilised Government would have resolved the matter through dialogue and negotiations.

I appreciate that people are entitled to different views on any topic. One must however distinguish between opinions, facts and untruths. In this regard, the statements in your article that the strike stemmed from an inadequate salary structure and that the Medical Association organised a general strike are examples of outright lies propagated by the government of the time.

I write this to clarify the truth and to set the record straight.

# EDITORIAL COMMENT

**DR WILFRED GALEA**

The 1977 – 1987 Doctors' strike was a painful chapter in Maltese Medical history which affected negatively all stakeholders: doctors who participated in the strike, doctors who remained in government employment and above all, patients.

The review of the book was written by the author from the author's point of view and the book complements other books by Dr Lino German and Prof. Charles Savona Ventura, which also dealt with the subject.

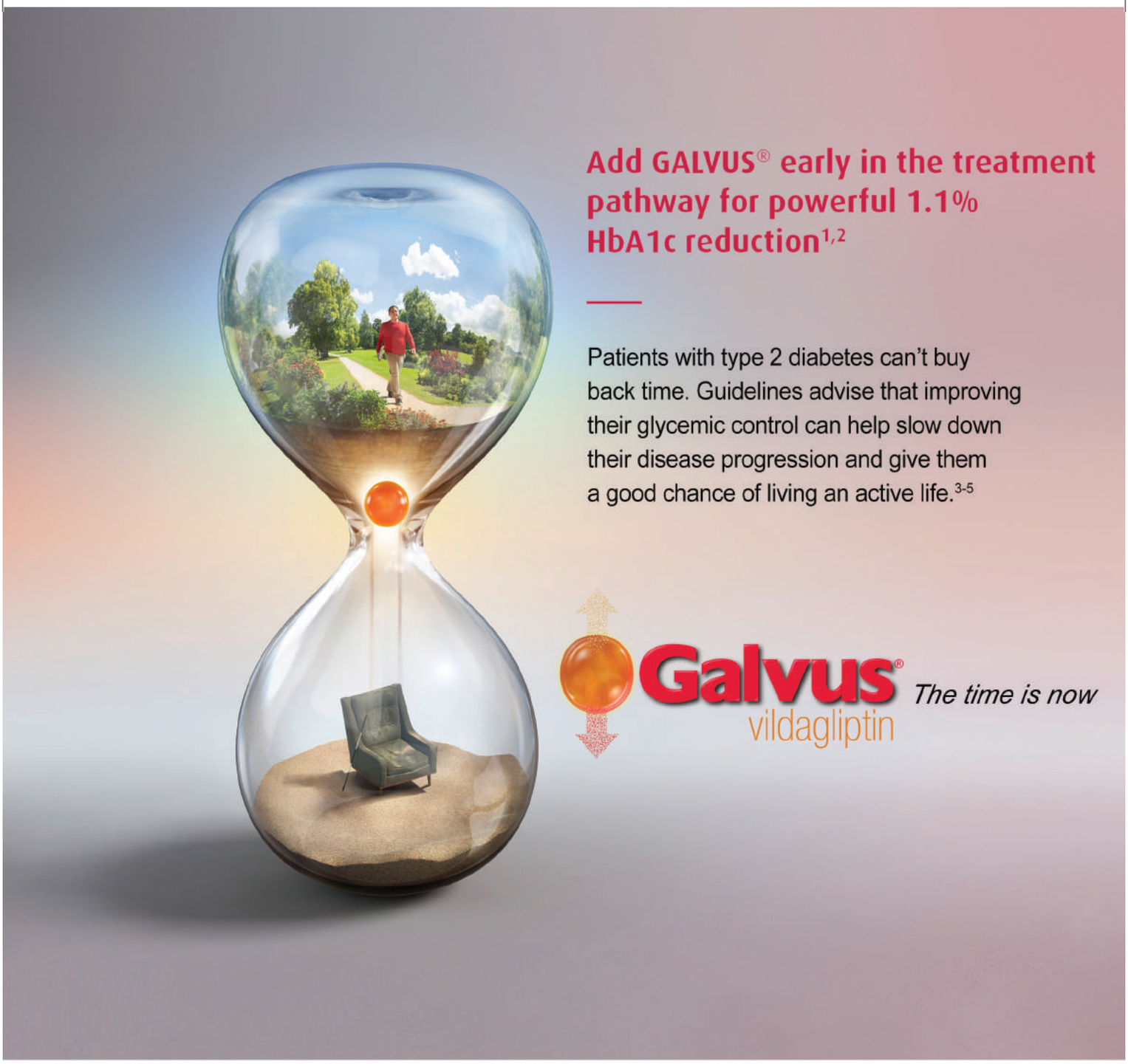
The strike also affected a cohort of medical students, myself included, who had to do their medical school years in Malta during the strike in a new and controversial 'student-worker' scheme and managed to graduate in spite of the system and many obstacles.

When these students graduated, they were looked down upon by some doctors who returned to Malta and were even labelled as 'gap doctors'.

I was fortunate enough to participate in the 'Family Medicine Faculty Training Programme' which was organised by the University of Toronto and University of Malta in 1988 but unfortunately this training programme was not repeated because of lack of support from the authorities at that time.

Fortunately, time is a great healer and there are colleagues from all generations who have consistently put aside all differences and continued to work for the benefit of the whole medical profession and patients in Malta.

*The discussion about this subject is now closed*



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Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. **DOSAGE:** When used as monotherapy in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea or in combination with insulin (with or without metformin), the recommended daily dose of Vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in dual combination with a sulphonylurea, the recommended dose is 50mg once daily in the morning. A lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. The safety and efficacy of Vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established. Galvus is not recommended for use in children and adolescents (< 18 years) as the safety and efficacy have not been established and no data are available. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. No dose adjustments are necessary in elderly patients (≥ 65 years). **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients **WARNINGS / PRECAUTIONS:** Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. There is limited experience in patients with ESRD on haemodialysis and Galvus should be used with caution in these patients. Galvus should be used with caution in patients with renal impairment. Galvus should not be used in patients with hepatic impairment. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. Clinical experience in patients with NYHA functional class I-III treated with Vildagliptin is still limited. There is no experience with NYHA class IV and therefore use of Vildagliptin is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. If pancreatitis is suspected, Vildagliptin should be discontinued; if acute pancreatitis is confirmed, Vildagliptin should not be restarted. Exercise caution in patients with a history of acute pancreatitis. Patients with Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or breast-feeding, since no studies on the effect on human fertility have been conducted for Galvus. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with Vildagliptin. As with other oral antidiabetic medicines, the hypoglycaemic effect of Vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors ADVERSE REACTIONS: Monotherapy: Common (>1/100 to <1/10): dizziness. Combination with metformin: Common: hypoglycaemia, tremor, headache, dizziness, nausea. Combination with sulphonylurea: Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Combination with Thiazolidinedione: Common: weight increase, oedema peripheral. Combination with insulin: Common: decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease. Combination with metformin and a sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia. For a full list of Adverse Reactions please refer to the SmPC. **LEGAL CATEGORY:** POM. **PACK SIZES:** 28 tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/003. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc. Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2018-MT-GAL-26-APR-2018

**Eucreas®**
**PRESENTATION:** Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus patients, indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea. Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control. DOSAGE: The dose of antihyperglycaemic therapy with Eucreas should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Eucreas may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy: The starting dose of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of vildagliptin and metformin as separate tablets: Eucreas should be initiated at the dose of vildagliptin and metformin already being taken. For patients inadequately controlled on dual combination with metformin and a sulphonylurea: The doses of Eucreas should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Eucreas is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose of Eucreas should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. Eucreas should be taken with or just after food to reduce gastrointestinal symptoms associated with metformin. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma. Severe renal failure (GFR < 30 ml/min). Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment, acute alcohol intoxication, alcoholism, lactation. **WARNINGS / PRECAUTIONS:** Eucreas is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. GFR should be assessed before treatment initiation and regularly thereafter. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued at the time of surgery under general, spinal or epidural anaesthesia and resumed no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. The IV administration of iodinated contrast agents can lead to contrast-induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal. A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.Eucreas should not be administered during pregnancy or lactation. Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia. The use of vildagliptin has been associated with a risk of developing acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis. There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol due to an increased risk of lactic acidosis, iodinated contrast agents, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics and products which can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. Vildagliptin Monotherapy: Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. Metformin monotherapy: Very common (>1/10): Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. Combination vildagliptin with metformin: Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. Combination with metformin and sulphonylurea: Common: hypoglycaemia, dizziness, tremor, hyperhidrosis, asthenia, decreased blood glucose, headache, chills. Combination with insulin: Decreased blood glucose, headache, chills, nausea, gastro-oesophageal reflux disease, diarrhoea, flatulence For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:** POM **PACK SIZES:** 30, 60 film-coated tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER:** EU/1/07/425/021, EU/1/07/425/027. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available upon request from: Novartis Pharma Services Inc. Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872. 2018-MT-EUC-23-APR-2018


**References:**
1. Novartis Europharm Ltd. Galvus Summary of Product Characteristics
2. Novartis Europharm Ltd. Eucreas Summary of Product Characteristics
3. Holman RR et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15):1577–1589.
4. Inzucchi SE et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38(1):140–149.
5. Garber AJ et al. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013; 19(2):327-336.


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