The nurse of the Mediterranean

Saviour Pisani

During the First World War Malta did not take an active part in the fighting. Britain was joined in an 'entente' a friendship agreement with France since 1904 and later with Russia in 1907. On the other hand Germany was allied to the Austrian-Hungerian Empire, hence when the Great War started in July 1914 there were France, Britain and Russia on one side and Germany and Austria-Hungary on the other. The British fleet "ruled the waves", hence with France and Britain as allies, to be joined later by Italy, the Mediterranean was more or less an allied lake, with Malta in the centre.

During the nineteenth century the Ottoman Empire was falling apart, and one of the big problems that faced the foreign office of Britain in the nineteenth century was the Ottoman Empire known as the sick man of Europe. Russia was looking at it from the part of the chief inhibitor of its demise, while Britain was taking the role of a doctor. Russia is a vast country, stretching from the Baltic to the Pacific and from the Arctic to the Black Sea. Its biggest problem was that it could not use its ports throughout the whole year. Its arctic port, the Archangel, was blocked by ice; its Baltic ports had a similar problem in winter. Furthermore the Baltic Sea was dominated by the German navy in XXXII. The latter was secondary to that of Britain. Russia's far eastern ports – Vladivostostock – was also frozen and far too distant. The Black Sea ports were closed by the Ottoman Empire during hostilities. The Russian ships had to pass through the Dardanelles to reach the Mediterranean and if the Dardanelles were under a hostile power no merchant ship could pass – i.e. the Russian navy was bottled up in the Black Sea.

Keywords
nurse, Mediterranean, first world war, Rupert Brooke

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The British were always suspicious of the Russian intentions towards the Ottoman Empire, and the Crimean War of 1854 was fought by Britain, France and the Ottoman Empire against Russia to destroy its main base of Sevastapol and its fleet. By the treaty of San Stefano and the convention of Berlin blocked by Bismarck, the small Balkan states of Bulgaria, Serbia, Rumania and Montenegro appeared and these showed that they were very jealous of their independence and were far more efficient than the decadent Ottoman Empire to thwart Russian ambitions to enter the Mediterranean Sea. Still the Balkans was not so stable and in 1911-1912 the Balkan Wars erupted. In 1914 after the Archduke Ferdinand was assassinated in Sarajevo, Austria-Hungary declared war on Serbia and the First World War started. The Ottoman Empire had a friendly relationship with Germany, its military was trained by Prussian officers and when the battle cruisers – Goeben and Breslan – were caught in the Mediterranean in July 1914 and sailed on to Constantinople where they were given as a present to the Sultan, the Ottoman Empire found itself on the German side together, incidentally with Bulgaria which felt short-changed by Serbia.

The First World War started in high spirits by both sides. However, it soon degenerated in trench warfare. The British old professional army, known as the old contemptible was soon decimated and new regiments came from Britain and its empire to replace the heavy losses. The French also lost many soldiers when they moved on Alsace and Lorraine, lost in 1870. The Russians lost thousands and thousands of soldiers in the battle of Tannenberg. Their equipment was found most wanting and it was clear to all military chiefs that Russia could not sustain a war of attrition. The soldiers went into battle without rifles, they had to pick rifles from dead or wounded colleagues as they advanced along the front. The Russian army needed munitions, heavy guns, transport, rifles and all that a modern war entails. The French knew that if the Russian front were to collapse – as it did later in the war, the full fury of the German army would be let loose on them. The only way available to supply them was by sea. The Baltic Sea was dominated by the German fleet, while the Archangel was hardly practical. Hence Winston Churchill, who was lord of the Admirality at that time, thought of supplying the Russian army from its Black Sea ports. To do this he had to open the Dardanelles to allied shipping, which really meant he had to knock the Ottoman empire out of the war. This he deemed a not so difficult task - after all the Ottoman Empire had been falling apart for more than a century, and it was kept in one piece thanks to the efforts of the British Government, the

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References: 1. IMS Health, NPA Plus™, October 2006 – 3 October 2008. 2. Data on file, MSD Cyprus and Malta. 3. Nauck MA, Meininger G, Sheng D, et al; for Sitagliptin Study Group 024. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared to the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007;9:194–205.

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Mark Muscat
Tuscany
acrylics on canvas, 23.5 x 18.0cm, July 2010

Dr Mark Muscat currently works as EUVAC.NET scientific co-ordinator at the Statens Serum Institut, Department of Epidemiology in Copenhagen, Denmark.

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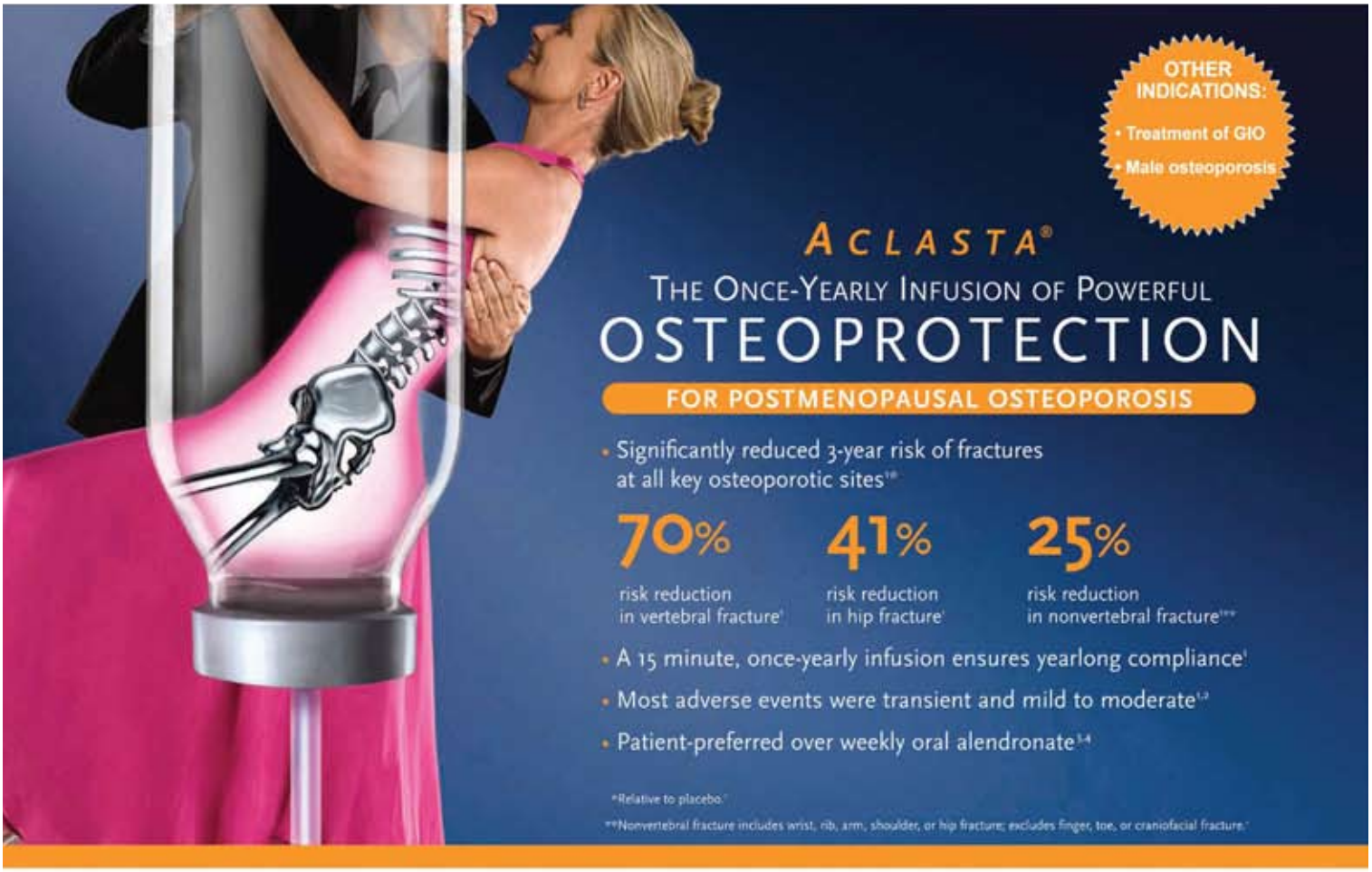

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CONTRAINDICATIONS: Hypersensitivity to zoledronic acid or to any of the excipients or to any bisphosphonate; hypocalcaemia; pregnancy; lactation.

PRECAUTIONS AND WARNINGS: Serum creatinine should be measured before each Aclasta dose. Aclasta should not be used in patients with creatinine clearance <35 ml/min. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function. Monitoring of serum creatinine should be considered in at-risk patients. Patients must be appropriately hydrated prior to administration of Aclasta, especially important for the elderly and for patients receiving diuretic therapy. Use with caution in conjunction with medicinal products that can impact renal function. A single dose of Aclasta should not exceed 5mg and the duration of infusion should be at least 15 minutes. Pre-existing hypocalcaemia and other disturbances of mineral metabolism must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. It is strongly advised that patients with Paget's disease receive supplemental calcium and vitamin D. Measurement of serum calcium before infusion is recommended for patients with Paget's disease. Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported with bisphosphonate therapy. A patient being treated with Zometa should not be treated with Aclasta. As a precaution against osteonecrosis of the jaw (ONJ) a dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Aclasta is not recommended in women of childbearing potential.

INTERACTIONS: Specific drug-drug interaction studies have not been conducted with zoledronic acid. Caution is recommended when Aclasta is used concomitantly with drugs that can significantly impact renal function, such as aminoglycosides and diuretics that can cause dehydration. In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase.

ADVERSE REACTIONS: The incidence of adverse reactions (e.g. fever, myalgia, flu-like symptoms, arthralgia and headache) are greatest with the first infusion and decrease markedly with subsequent infusions. The majority of these reactions occur within the first three days and were mild to moderate and resolved within three days of the event onset. The incidence of these adverse reactions can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration. Very common: Fever. Common: Flu-like symptoms, chills, fatigue, pain, asthenia, malaise, arthralgia, myalgia, bone pain, back pain, pain in extremity, vomiting, nausea, headache, dizziness, atrial fibrillation, hypocalcaemia†, ocular hyperaemia, diarrhoea, increased C-reactive protein, infusion site reactions. Uncommon: Hypertension, flushing, palpitations and others. Not known: Scleritis, orbital inflammation, hypotension, renal impairment, osteonecrosis of the jaw, dehydration secondary to post dose symptoms, hypersensitivity reactions
† *Common in Paget's disease only.* Please refer to SmPC for a full list of adverse events.

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References: **1.** Aclasta SmPC. Novartis Europharm Ltd. **2.** Black DM, Delmas PD, Eastell R, et al; for the HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809-1822. **3.** Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone. 2007;40:1238-1243. **4.** McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone. 2007;41:122-128.

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Publish or perish?

This issue of the Malta Medical Journal contains a historical perspective on medical publications in Malta over the years and it is a tribute to the medical community that over the last one hundred and seventy years, dedicated members of that profession have published articles of relevance to the practice of medicine in the Maltese Islands. The aim has been to highlight problems particular to the epidemiology, pathophysiology and management of disease endemic in Malta.

In a country with a population of just over 400,000, the survival of such publications has depended on a number of different factors – infrastructural, financial, and by the very nature of their content, relatively limited circulation with the resultant implications for indexing and the acquisition of an impact factor. Ultimately until recently the limited resources available to local researchers wishing to address specific hypotheses with the aim of improving patient centred medical care also impacted on the volume of scientific activity going on.

In this issue, there are articles related to chronic non communicable disease which are having a significant impact on patient morbidity and mortality and the healthcare budget namely chronic respiratory problems and dementia. The provision of cost effective healthcare with rehabilitation and devolvement of patient care to the community represent major public health challenges at present and the identification of lacunae in service provision is the initial step in the development of national health strategies in chronic non-communicable diseases such as these two. The implementation of such strategies mandates the use of auditing and of analysis re local concordance with international established standards of health care. Genetic, cultural and health service structures differ in individual countries and in specific regions in individual countries. Hence the need to ensure that proposed measures and treatments are appropriate to the specific population in this case the Maltese population.

Subsequent to the establishment of postgraduate training programs, young trainees are now keen to research and publish and the Faculty of Medicine now has seen a significant increase in the number of students undertaking Masters and Doctoral studies. It is now possible to apply for research funds and a number of courses are available that focus on grantsmanship, research, statistics and scientific writing. The Malta Medical Journal which is published online and also in hard copy, provides such young researchers with a forum to publish their observations, under the supervision and with the help of their more senior colleagues.

This increase in research activity and publication will hopefully continue to increase over the coming years reflecting the local medical community's healthy constructive critical attitude to work published in the international medical community and its relevance to the practice of medicine in Malta.

Josanne Vassallo
Editor

Review Article

Pharmacotherapeutic aspects of dementia care in Malta

Charles Scerri, Stephen Abela, Anthea Innes

Abstract

Dementia is the most common neurodegenerative disorder of old age affecting one percent of the local general population. It is a major predictor of morbidity and mortality in the elderly, adding a significant burden on health and social care systems across Europe. The financial impact of caring for individuals with dementia is considerable and progressive loss of cognitive function does not only pose challenges to the patients but also adds significant strain on the well-being of caregivers and family members. Although no cure is available, disease progression can be delayed by early intervention and by the use of pharmacotherapeutic agents that interfere with central neurotransmitter systems involved in cognitive processes. This review presents current trends in pharmacotherapeutic intervention in dementia care together with caregiver perceptions on treatment expectations in Malta.

Keywords

Dementia, Malta, caregivers, pharmacotherapy

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Introduction

Dementia is a complex clinical syndrome associated with behavioural, cognitive and personality changes. It usually presents itself as impairment in memory, abstract thinking, impaired judgment and other disturbances that are of such severity that they interfere with work and social activities.[1] Several diseases are known to cause dementia. Alzheimer's disease (AD) accounts for 50-70% of cases followed by Vascular dementia, Lewy Body Disease, fronto-temporal dementia and dementia secondary to disease.[2] According to an estimate from World Health Organization (WHO), dementia is responsible for more years lived with disability in people older than 60 years (11.2%) than stroke (9.5%), cardiovascular disease (5%) or all forms of cancer (2.4%).[3] Currently, there are more than 7.3 million people with dementia in Europe, a figure that is expected to double by the next 30 years.[4] This will result in a growing burden on health care resources and family members who, in the majority of cases, provide informal care at home. A recent study estimated that approximately one percent of the general population in Malta has dementia, a figure that is expected to increase significantly by the year 2050 (Table 1).[5]

Over the last two decades, a number of therapeutic strategies have been developed for the symptomatic management of the most common forms of dementia, particularly AD. The latter is characterised by the presence of amyloid plaques and neurofibrillary tangles coupled with significant degeneration of the central cholinergic system resulting in cognitive decline.[6] Indeed, the first pharmacological agents to be approved for symptomatic treatment of AD were the acetylcholinesterase inhibitors which mainly block the enzyme acetylcholinesterase thus increasing the concentrations of the neurotransmitter acetylcholine in the synaptic area (Table 3). Studies showed that the use of these drugs (namely donepezil, galantamine and rivastigmine) significantly improved cognition and activities of daily living.[7] Another drug that is also available in the therapeutic management of AD is the glutamatergic-system modifier memantine which partially blocks glutamate-induced overstimulation of the N-methyl-D-aspartate (NMDA) receptor thus reducing calcium-induced cytotoxicity (Table 3). In randomised clinical trials, this drug demonstrated the ability to delay cognitive and functional decline without any significant incidence of side effects.[8,9] According to the latest guidelines issued by the UK National Institute for Clinical Excellence (NICE), acetylcholinesterase inhibitors should be recommended for use in moderate AD whereas memantine should

Table 1: *Current and projected number of total dementia cases in the Maltese islands (adapted from Abela et al).*[5]

Year	30-59	60-64	65-69	70-74	75+	Total cases	% of total population
2010	203	293	316	629	2947	4388	1.12
2015	204	268	444	749	3227	4892	1.25
2020	201	285	404	1035	3660	5585	1.44
2025	201	253	422	931	4538	6345	1.66
2035	190	257	332	881	5161	6821	1.91
2050	150	268	414	970	4567	6369	2

only be considered for clinical trials.[10] Apart from Malta and Latvia, all EU-member states offer some form of financial reimbursement to any of these classes of anti-dementia drugs.

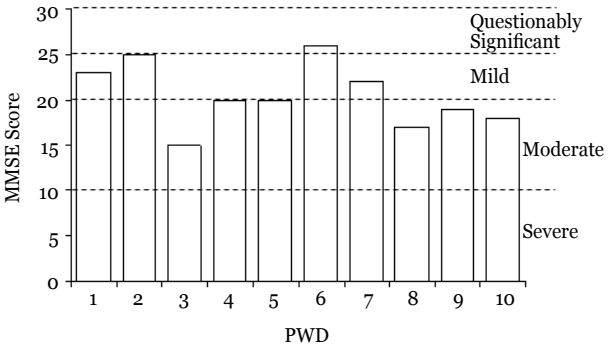
In recent years, strategies on dementia care have also been developed in parallel with pharmacotherapeutic research since caregivers suffer from high rates of physical and mental disorders including anxiety and depression.[11] Caregivers are also generally excluded in providing their views on the effectiveness of anti-dementia pharmacotherapy in ameliorating the symptoms as most research is focused on the disease model. A recent review study found that not one of the 63 papers (listed in medical databases) reporting on the effectiveness of drug treatments included the carer perspective.[12] Indeed, the carer perspective becomes important in assessing the effectiveness of a particular anti-dementia pharmacotherapeutic regimen in enhancing the quality of life and assessing caregiver burden.[13] The input of carers would also be instrumental in providing qualitative information that should aid medical professionals to adjust therapy ensuring better pharmacotherapeutic outcomes.

Hospital-based pharmacotherapeutic management

In Malta, no research has yet been carried out on the use of pharmacotherapeutic agents in treating the various symptoms observed in dementia. In order to have an indication on the use of anti-dementia drugs in a local hospital-based clinic, a small scale exercise involving ten persons with dementia was conducted in October 2008. Also involved were seventeen caregivers, the latter comprising five spouse carers (two husbands and three wives), nine children (eight daughters and one son) and three daughter-in-laws. The sample of potential caregivers was selected from the Zammit Clapp Hospital Memory Clinic and was subsequently interviewed by a member of the research team. All participants had to be caring for a relative who had a formal diagnosis of dementia, who was attending the Memory Clinic, who continued to live in the community and who was over 65 years of age. The medical history of individuals with dementia was analysed for parameters including Mini Mental Scale Examination (MMSE) scores (which classify dementia into mild, moderate and severe), date of first attendance to the Memory Clinic, date of diagnosis, medical conditions besides dementia and pharmacotherapy. Ethical approval was obtained from three sources prior to conducting the interviews with caregivers. These included the University of Stirling (UK) Ethics Committee, the University of Malta Research Ethics Committee and the Malta Health Department. All relatives participating in the study received a written information sheet prior to consenting to participate and this was also discussed verbally prior to obtaining written consent.

The results showed that more than half of the persons with dementia participating in the exercise had the moderate form of dementia in which there is clear impairment of cognitive function that may require continuous supervision (Figure 1). The rest of the patients had mild or questionably significant deficits in which the person with dementia continues to function normally with support and assistance. No patient had a Mini Mental State Examination score of less than 10 denoting the severe form of the condition which requires continuous supervision and assistance in their Activities of Daily Living (ADL). Table 2 shows the time intervals from when the person with dementia visited the Memory Clinic for the first time until diagnosis of dementia and initiation of treatment was performed. The mean number of days elapsed from first visit to diagnosis was that of 41.3±19.3 (mean±SEM) days. The majority of patients had their diagnosis of dementia during their first visit to the clinic. The mean number of days elapsed from diagnosis till the initiation of treatment was that of 69.4±42.3 (mean±SEM) days with most patients prescribed anti-dementia medication on the day of diagnosis. The mean total number of elapsed days from the patient first visit to the clinic till the initiation of treatment was of 108.3±34.9 (mean±SEM) days. Figure 2 shows the percentage of other pathological disorders in conjunction with dementia (taken as 100% to signify that all patients participating in this exercise had dementia). Most of the patients had depression and a significant number had diabetes, hypertension and hypecholesterolaemia. Other less common comorbidities included gout, anxiety, hearing loss and previous surgical interventions prior to dementia diagnosis. Figure 3a shows the amount of drugs prescribed for every person with dementia. The total number of drugs prescribed was 59 giving an average of 5.9 drugs per patient. The majority of patients were prescribed four or more drugs. All persons with dementia, except one,

Figure 1: *Minimental State Examination (MMSE) scores for each person with dementia (PWD) participating in the exercise together with interpretation of the scores according to Folstein et al.*[29]



Score	Degree of impairment	Day-to-day functioning
25 to 30	Questionably significant	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living
20 to 25	Mild	Significant effect. May require some supervision, support and assistance
10 to 20	Moderate	Clear impairment. May require 24-hour supervision
0 to 10	Severe	Marked impairment. Likely to require 24-hour supervision and assistance with ADL

were prescribed anti-dementia pharmacotherapy which mainly consisted of the acetylcholinesterase inhibitor galantamine and the partial NMDA receptor antagonist memantine. A total of fifty drugs were used to control other coexisting medical conditions with the majority being cardiovascular agents followed by antidiabetics, antidepressants and lipid lowering agents. Supplements and vitamins were prescribed in a number of cases whereas antipsychotics were used in one of the patients (Figure 3b).

The qualitative interviews with seventeen caregivers showed a lack of perceived support by carers when caring for a person with dementia. The majority of participants mentioned the lack of professional healthcare services specifically aimed for patients with cognitive difficulties. Most importantly, caregivers reported the significant financial costs involved in the purchase of anti-dementia medication since dementia is not included among the conditions listed in the Fifth Schedule of the Malta Social Security Act. It was also observed that relatives are ambivalent as to the effectiveness of these drugs but they were unwilling to discontinue treatment in case it made caregiving more difficult or that the symptoms will worsen. This is reported in detail elsewhere.[14]

Discussion

Dementia is an ever-growing condition that is associated with significant social, physical, psychological and psychiatric disability not only in individuals diagnosed with the illness but also in caregivers and family members. Up until recently, there was no effective pharmacotherapeutic intervention to manage the cognitive symptoms associated with dementia.[10] Although the benefits of current treatments are deemed to be modest in that they do not halt the disease progression, they represent a major step forward in the clinical management of these patients.[12] Although the presented small scale exercise

Table 2: *Time intervals from first visit to initial diagnosis and treatment for each person with dementia (PWD) participating in the exercise (* signifies diagnosis of dementia during the first visit at the Memory Clinic, ** signifies initiation of treatment on the same day of dementia diagnosis).*

PWD	Days elapsed from first visit to diagnosis	Days elapsed from diagnosis to initiation of treatment	Total number of days from first visit to initiation of treatment
1	111	0**	111
2	n/a	n/a	n/a
3	0*	306	306
4	90	0**	90
5	26	0**	26
6	0*	77	77
7	0*	103	103
8	0*	n/a	n/a
9	145	0**	145
10	0*	n/a	n/a

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It is recommended that individuals who receive a first dose of Silgard complete the 3 dose vaccination course with Silgard (see section 4.4). **CONTRA-INDICATIONS:** Hypersensitivity to the active substances or to any of the excipients. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Silgard should not receive further doses of Silgard. Administration of Silgard should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a mild upper respiratory tract infection or low-grade fever, is not a contraindication for immunisation. **PRECAUTIONS:** As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine. Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with Silgard (See section 4.8). Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of Silgard. As with any vaccine, vaccination with Silgard may not result in protection in all vaccine recipients. Silgard will only protect against diseases that are caused by HPV types 6, 11, 16 and 18 and to a limited extent against diseases caused by certain related HPV types (See section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used. Silgard is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Silgard has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer, high-grade cervical, vulvar and vaginal dysplastic lesions or genital warts. It is also not intended to prevent progression of other established HPV-related lesions. Silgard does not prevent lesions due to a vaccine HPV type in women already infected with that HPV type at the time of vaccination (see section 5.1). The use of Silgard in adult women should take into consideration the variability of HPV type prevalence in different geographical areas. In the clinical study of adult women (24 to 45 years of age), no statistically significant vaccine efficacy was observed after 2.2 years of follow-up in the full analysis set that includes women regardless of baseline HPV status (see section 5.1). The decision to vaccinate an individual woman 27 to 45 years old should take into account her risk for previous HPV exposure and her potential benefit from vaccination. Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100 % effective and Silgard will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations. There are no data on the use of Silgard in individuals with impaired immune responsiveness. Individuals with impaired immune responsiveness, whether due to the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may not respond to the vaccine. This vaccine should be given with caution to individuals with thrombocytopaenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals. The duration of protection is currently unknown. Sustained protective efficacy has been observed for 4.5 years after completion of the 3-dose series. Longer term follow-up studies are ongoing (see section 5.1). There are no safety, immunogenicity or efficacy data to support interchangeability of Silgard with other HPV vaccines. **SIDE EFFECTS:** Refer to SPC for complete information on side effects. The following vaccine-related adverse reactions were observed among recipients of Silgard at a frequency of at least 1.0 % and also at a greater frequency than observed among placebo recipients. They are ranked under headings of frequency using the following convention: [Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000), including isolated reports] Musculoskeletal and Connective Tissue Disorders: Common: pain in extremity. General disorders and administration site conditions: Very common: pyrexia. Very common: at the injection site: erythema, pain, swelling. Common: at the injection site: bruising, pruritus. In addition, in clinical trials adverse reactions that were judged to be vaccine- or placebo-related by the study investigator were observed at frequencies lower than 1 %: Respiratory, thoracic and mediastinal disorders: Very rare: bronchospasm. Skin and subcutaneous tissue disorder: Rare: urticaria. Nine cases (0. 07 %) of urticaria were reported in the Silgard group and 16 cases (0.14 %) were seen in the adjuvant-containing placebo group. **Post Marketing Experience:** Post Marketing adverse events have been spontaneously reported for Silgard and are not listed above. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure. Blood and lymphatic system disorders: lymphadenopathy. Immune system disorders: hypersensitivity reactions including anaphylactic/anaphylactoid reactions. Nervous system disorders: Guillain-Barré syndrome, dizziness, headache, syncope sometimes accompanied by tonic-clonic movements. Gastrointestinal disorders: nausea, vomiting. **Musculoskeletal and connective tissue disorders:** arthralgia, myalgia. General disorders and administration site conditions: asthenia, chills, fatigue, malaise. **Marketing Authorisation Number:** EU/1/06/358/007. **Marketing Authorisation Holder** Merck Sharp & Dohme Limited. Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK. **POM:** Date of review of prescribing information: Sep 2009. **TM** denotes registered trademark of Merck & Co. Inc.. API.GRD.09

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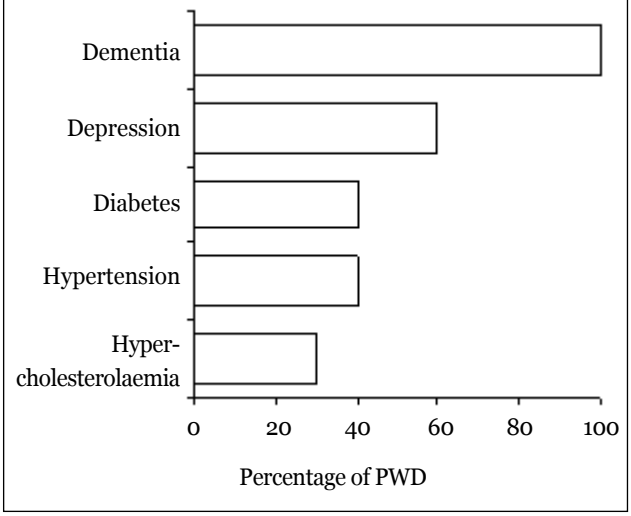
has its limitations in terms of the number of subjects involved, the general trend observed indicate that at the Zammit Clapp Hospital Memory Clinic, patients are mostly diagnosed early upon their first clinical appointment, are mostly managed with acetylcholinesterase inhibitors and usually suffer from other comorbities which may or may not be related to dementia. Furthermore, the overall feeling of caregivers and family members is that they are being left out from decisions on pharmacotherapy prescribed for patients with dementia under their care.

Various studies suggest that pharmacotherapeutic intervention with anti-dementia medication early in the disease process may slow down the disease progression and thus improve the quality of life for both patient and caregivers.[15] Although this exercise did not examine the time lapse prior to seeking clinical advice following the emergence of the first symptoms, it is clear that most of the patients did not seek medical intervention early and thus the majority were in the moderate stages of the disease. Reasons for such delay may include caregiver's lack of knowledge or reluctance to seek help, and patient, family, and physician-related factors.[16] In participating patients, pharmacotherapeutic dementia-related intervention consisted of the use of both acetylcholinesterase inhibitors and glutamatergic-system modifiers. Whether the use of these agents had any significant effect on delaying the disease progression or controlling the behavioural symptoms of our patients is unclear and was beyond the scope of this exercise.

Figure 2: *Most common comorbid disorders in PWD participating in the exercise.*



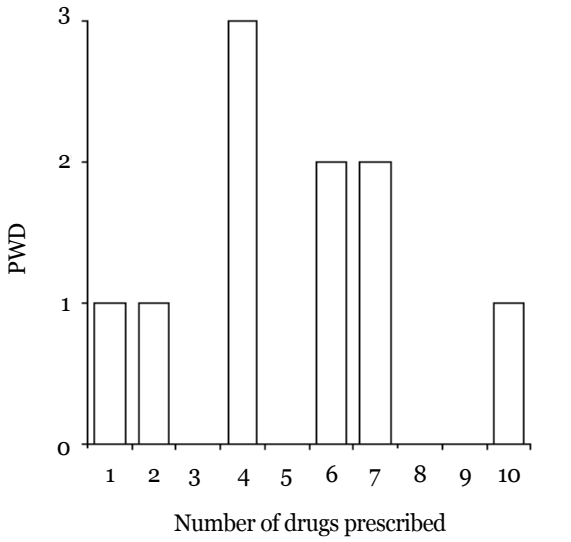
Acetylcholinesterase inhibitors were the first pharmacological treatment approved for symptomatic treatment of AD. These drugs have been found to stabilise the cognitive decline for up to 3-6 months.[17,18] Memantine, the only glutamatergic system modifier approved for the treatment of AD, was also reported to improve dementia symptoms by reducing the rate of clinical deterioration among patients with moderate to severe AD.[9,19] Currently there is a strong debate on the cost effectiveness of the

Table 3. *Characteristics of pharmacotherapeutic agents used in the management of Alzheimer's disease (AChEI: acetylcholinesterase inhibitor, AD: Alzheimer's disease, nAChRs: nicotinic acetylcholine receptors, NMDA: N-methyl-D-aspartate).*[28]

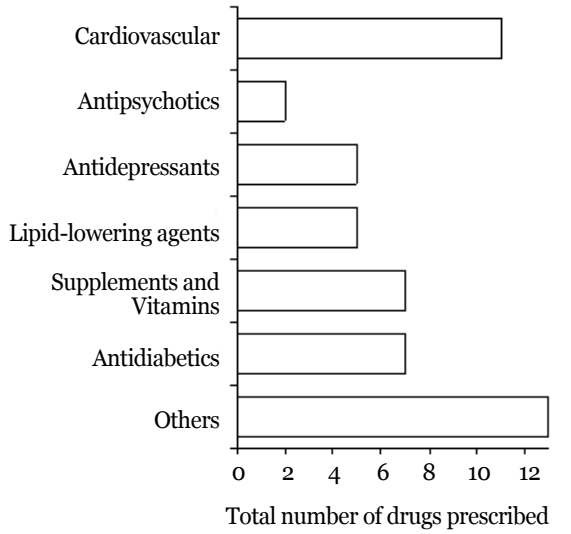
Medication	Pharmacological class	Mode of action	Recommended use	Potential adverse effects
Donepezil hydrochloride (Aricept®)	AChEI	Block acetylcholinesterase enzyme	Mild-to-moderate AD	Anorexia, diarrhoea, dreams, fatigue, insomnia, muscle cramps, nausea, vomiting, weight loss
Rivastigmine tartrate (Exelon®)	AChEI	Block both acetyl- and butyryl-cholinesterase enzymes	Mild-to-moderate AD	Anorexia, diarrhoea, nausea, vomiting, weight loss
Galantamine hydrobromide (Reminyl®)	AChEI	Block acetylcholinesterase enzyme. Allosterically stimulates nAChRs	Mild-to-moderate AD	Anorexia, nausea, vomiting, weight loss
Memantine hydrochloride (Axura®, Ebixa®)	Glutamatergic system modifier	Partial NMDA receptor antagonist	Moderate-to-severe AD	Agitation, constipation, dizziness, hallucinations, headache, insomnia

Figure 3: *Number of PWD on polypharmacy (a) and total number of drugs prescribed to all patients as per drug mode of action or therapeutic class (b).*

a.



b.



widespread use of these drugs for the various stages of AD. The National Institute of Clinical Excellence (NICE) recommends the use of acetylcholinesterase inhibitors in the moderate stages of the disease with the use of memantine reserved only for clinical trials.[10] This decision was widely criticised by the Royal College of Psychiatrists, the British Geriatric Society and the Royal College of Nursing as well as by various EU-based dementia societies. In Malta, no such recommendations exist and both classes of drugs can be prescribed by general practioners and specialists. Interestingly, the trend observed indicated that half of the participating patients were recommended with the use of anti-dementia drugs upon diagnosis during their first visit at the Memory Clinic, irrespective of the severity of the condition. This prescribing behaviour is in concordance with current recommendations denoting that early initiation of therapy is associated with greater long-term benefits.[20]

A significant number of participating patients were diagnosed with depressive illness possibly indicating a high prevalence rate of depression in patients with dementia. This was also reflected by the significant use of antidepressants as part of the overall prescribed treatment regimen. Epidemiological studies show a possible pathological association between the two conditions, with depression possibly acting as a prodromal sign or early symptom of AD.[21] Due to the limited number of patients participating in this exercise, it was not possible to investigate any link between depression and dementia although this would be an interesting research area for future consideration. The same is also valid with the other main pathologies observed. Although cardiovascular disease, diabetes and hypercholesterolaemia are risk factors in vascular dementia, these conditions are also prevalent in old age.

The use of multiple medication (polypharmacy) in the elderly has always been regarded as a complex issue in pharmaco-geriatric management. Although polypharmacy may be the only choice in some individuals, multiple medication use may increase the risk of non-compliance, medication error and potentially adverse drug interactions.[22] Prescribing for elderly patients with dementia proves to be even more challenging due to the changing needs that accompany cognitive decline and related behavioural symptoms.[23] Furthermore, more medications may be indicated in patients with dementia due to the presence of other pathologies which are common in old age.[24] Our data indicated that, on average, each person with dementia was prescribed with more than five different medications for the management of dementia and other comorbidities. This finding raises important clinical concerns, especially for individuals who still live in the community, in some cases on their own. Furthermore, because the use of polypharmacy increases the risk of falls, prescribing unnecessary medication may further enhance institutionalisation. Polypharmacy is also associated with increased risk of adverse drug-drug interactions which can have potential life-threatening consequences in older adults. This is especially critical in patients with dementia who are cognitively impaired and therefore not be able to explain or self report the symptoms. Interestingly, only one drug (lorazepam) was found to be part of the Beers Criteria,[25] a list of medications that are generally considered to be inappropriate when given to the elderly. No potentially serious drug-drug interactions were observed. In line with guidelines issued by NICE,[10] prescription of antipsychotic drugs was only present in one participating patient attending the Memory Clinic. Recent data shows that the use of these drugs in persons with dementia is associated with an increase in the risk of fatality.[26]

Studies including the views and experiences of caregivers on the effectiveness of anti-dementia drugs are lacking with a major focus directed towards conventional scientific evidence which is mostly relevant to clinicians and research scientists.

This lack of caregiver perspective was apparent in our qualitative assessment of the participating subjects. Caregivers were mostly concerned with the lack of support from the central health authorities in caring for their relatives. The greatest concern is the lack of financial assistance in purchasing anti-dementia medication which, in some cases, can take up a third of the person with dementia pension. Together with Latvia, Malta is the only country where the health authorities do not offer any form of financial support in accessing these drugs.[27] Even though some caregivers interviewed were unsure of the efficacy of anti-dementia medication in slowing the disease progression, they were unwilling to stop treatment.

Conclusion

Although more research is needed, using a larger sample number, the trends observed highlight the need for a nationwide strategy that includes the various aspects involved in pharmacological and non-pharmacological management of dementia. Such strategy should include the views of policy makers, healthcare professionals as well as patients and their caregivers with the aim of designing and implementing a series of recommendations that that should enhance high-quality dementia care in Malta.

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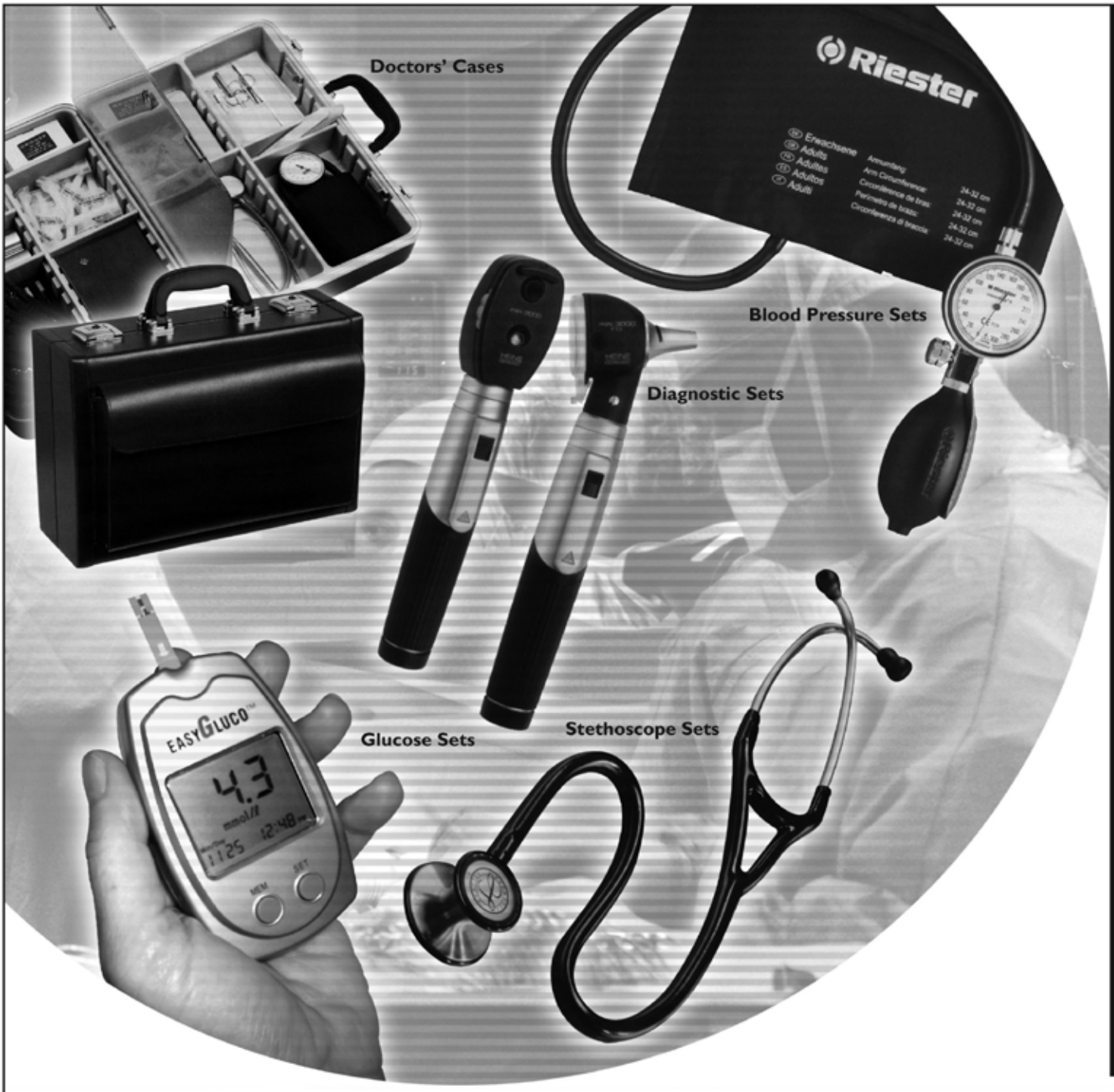

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Review Article

Pulmonary rehabilitation: insight into current trends

Anabel Sciriha, Stephen Montefort

Abstract

Pulmonary rehabilitation is a widely accepted therapeutic tool used to improve the quality of life and functional capacity of individuals with chronic lung disease. It is a multidisciplinary, comprehensive program designed to optimise autonomy and physical performance in patients with chronic respiratory impairment. There is sufficient evidence to support the use of pulmonary rehabilitation for a subset of patients and to indicate that it can improve exercise tolerance and symptoms of dyspnoea, as well as enhance health-related quality of life of patients with COPD and other respiratory conditions. According to projections in the Global Burden of Disease Study, COPD will be the fifth leading cause of disability-adjusted-life-year loss worldwide in 2020.

The goal of pulmonary rehabilitation is to help the individual achieve the highest level of independent functioning by improving pulmonary function, increasing exercise endurance and exercise work capacity, reducing dyspnoea and normalising blood gases.

Locally, no pulmonary rehabilitation service as described by respiratory societies is offered. Therefore, this paper will look into the current research focusing on future recommendations for this service in the international setting with an aim of implementing this into the local health care system.

Keywords

Asthma, COPD, Pulmonary rehabilitation, chronic, acute

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Introduction

Rehabilitation is the restoration of individuals to the fullest medical, mental, emotional, social and vocational potential the individual is capable of. The basic premise of all rehabilitation is that it is possible to effect positive change under the poorest circumstances imaginable and that no effect of illness save for death is absolute.[1]

Pulmonary rehabilitation is defined as a program for people who have chronic lung disease.[2] Its primary goal is to enable people to achieve and maintain their maximum level of independence and functioning. Although most pulmonary rehabilitation programs focus on people who have chronic obstructive pulmonary disease,[2] people with other types of lung disease may benefit as well. The most successful rehabilitation programs are those in which services are provided by a physiotherapist, nurse, doctor, psychologist or social worker, and a dietitian working as the pulmonary rehabilitation team to coordinate complex medical services.[3]

Optimal length of the rehabilitation phase

Despite the increasing propagation of the efficacy of pulmonary rehabilitation, there is no definitive proposal for the best training strategy[2-4] with variances in the duration and frequency.[5,6] Significant gains in exercise tolerance, dyspnoea, and quality of life have been observed following rehabilitation programs as short as 10 days[7] and others as long as 18 months[8] with gains in exercise tolerance reported to be greater in the latter.[9] Two randomised trials compared 3 months and 18 months of low-intensity exercise training. The longer intervention led to 6% increase in the 6 minute walk distance, 12% reduction in self-reported disability and faster completion of stair climbing and overhead tasks.[10] No differences though were seen in pulmonary function studies between groups, after training. The investigators concluded that the benefits achieved after short-term pulmonary rehabilitation began to decay once the intervention was terminated, despite encouragement to continue participation in a home-based or community-based programme. On the other hand, Foy *et al* [11] showed that only male patients achieved greater gains in Chronic Respiratory Disease Questionnaire scores following the 18-month program (compared to 3 months). In fact, more favourable scores than those in the short-term group were reported for dyspnoea, fatigue, emotional function and task mastery.

In a 2005 published prospective trial[12] involving seven outpatient programmes, patients achieved significant gains in exercise tolerance (6 minute walk distance), dyspnoea and

health status (Medical Outcomes Study 36-item Short Form and quality-of-life index) after 12 weeks of pulmonary rehabilitation. Following an additional 12 weeks of rehabilitation, exercise tolerance, but not health status or dyspnoea, outcomes improved further, suggesting that programme duration may not impact all outcomes equally. Also, in support of longer term exercise training, 6-month outpatient pulmonary rehabilitation programmes composed of moderate-to-high-intensity aerobic and strength exercise training led to significant improvements in exercise performance and quality of life.[13] Although this study did not compare the 6-month programme with a shorter one, the benefits gained following the 6-month training program persisted 18 months after the completion of rehabilitation.

Severe COPD patients were also found to achieve greater improvements in treadmill endurance, incremental shuttle walk distance, and quality of life following a 7-week outpatient pulmonary rehabilitation programme compared with an identical program of only 4 weeks duration. However, patients who underwent the 4-week programme were not reassessed at the 7-week time point to enable the direct comparison of outcomes.[9]

Overall, although some studies suggest that the duration of the pulmonary rehabilitation programme impacts exercise tolerance improvement, it is less clear that other outcomes such as health status or dyspnoea are similarly affected by programme duration. Randomised controlled trials have shown that short-term pulmonary rehabilitation (4 to 12 weeks) can reduce the number of hospitalisations, improve quality of life, reduce respiratory symptoms, improve exercise tolerance, increase self-efficacy, and improve the ability to perform activities of daily living. However, only a few studies have looked at the benefits of long-term (12 weeks or more) supervised pulmonary rehabilitation (Table 1).

It has not been established to what degree the benefits of short-term pulmonary rehabilitation diminish over time, how long these benefits persist with continued supervised intervention, or the optimal nature of long-term pulmonary rehabilitation intervention. The confounding effects of multiple study designs including varying durations of exercise, education, breathing retraining, and home exercise interventions have hindered solid conclusions about these issues.

Rehabilitation in the acute and chronic phase

Acute exacerbations of COPD represent a major burden for patients and health care systems.[13,14] They are a common reason for hospital admissions and severely affect health-related quality of life[15] and prognosis.[16] Mortality rates during hospitalisations are around 10%[17] and during the following year hospitalisation may be as high as 40%. From the health care provider's perspective, COPD is resource consuming[18] and about 10% of COPD patients suffering from acute exacerbations account for over 70 percent of costs caused by COPD, primarily due to emergency visits and hospitalisations.

Position papers of the American College of Physicians and American College of Chest Physicians provide recommendations on the management of acute exacerbations. However, no recommendations on how future exacerbations and hospitalisations could be prevented are indicated, despite this being one of the main goals of COPD management. One solution that has been adopted in clinical practice is to provide rehabilitative care after treatment of acute exacerbation including physical exercise, patient education focusing on self-management strategies and psychosocial support.

The rationale to offer rehabilitation in patients recently treated for acute exacerbation is to enhance quality of life, as in stable COPD patients[14] and modify factors associated with increased risk for post-exacerbation morbidity and mortality. Patients with frequent exacerbations have more pronounced skeletal muscle weakness and a more limited six minute walking distance, which is in turn a risk factor for exacerbations and mortality. Thus, respiratory rehabilitation may have the potential to reduce hospital admissions by improving exercise capacity. It is surprising that research on the effects of respiratory rehabilitation in patients after acute exacerbations, is very scant.

Randomised controlled trials evaluating the effects of pulmonary rehabilitation after hospitalisation for acute exacerbations of COPD,[19] report improvements in outcome measures at three months after hospital discharge with significant improvements in walking distance (p=0.0002), health status scores (p=0.002), all four domains of the Chronic Respiratory Questionnaire (dyspnoea, p=0.003; fatigue, p=0.004; emotion, p=0.008; mastery of tasks, p<0.001). Therefore, this trend showed that early intervention with pulmonary rehabilitation after a hospital admission for acute exacerbations of COPD is safe and leads to statistically and clinically significant short-term improvements in exercise capacity and health status.[19]

Compared to rehabilitation during stable periods, the effects of rehabilitation tend to be larger after acute exacerbations. Studies looking at the acute phase are relatively small in sample size, therefore there is the tendency to overestimate the effect of an intervention compared to large trials. Also, methodological limitations were found and one cannot exclude that the estimates provided by the meta-analyses represent overestimations of the effect of respiratory rehabilitation after acute exacerbation. Therefore, larger trials seem justified to challenge the data available.

When conducting studies post acute exacerbations, recruitment of patients may be difficult because not all of them may want to be randomly allocated to respiratory rehabilitation or conventional care, in a situation of poor health status. It must also be taken into consideration that exercise capacity is particularly low after acute exacerbations, and therefore the exercise programme should be designed carefully. Strength exercise and tolerable whole body exercise modalities such as interval exercise may be particularly suitable for these patients.[19] Rehabilitation may not only reduce the number of acute exacerbations, but also their severity. Patients may learn to notice imminent exacerbations and seek medical attention earlier leading to a shift from inpatient to the less costly outpatient treatment of acute exacerbations. The significant reduction in hospital readmissions is suggestive of a beneficial cost-benefit balance.

Table 1: *Reported durations and outcomes of pulmonary rehabilitation programmes. (RCT: randomized clinical trial; OP: outpatient, PRP: pulmonary rehabilitation programme, QOL: quality of life; PF: pulmonary function; NS: not significant)*

Duration of Pulmonary Rehabilitation

Study/ year	Study type	Country/Setting	No of Patients	Outcomes/results
Troosters *et al.* 2000	RCT: 6 *vs* 18 months *vs* usual care	Belgium/OP	100	Pulmonary function; exercise capacity; muscle strength; QOL Walking distance ($p<0.05$);exercise capacity ($p<0.02$); no significant effects of training programme on PF measures *vs* usual care; improved quadriceps strength ($p<0.05$) and QOL ($p< 0.001$)
Foy *et al.* 2001	RCT: short- *vs* long-term PRP	United States/OP	140	Four domains of CRQ. Significant changes in short *vs* long term in all domains
Green *et al.* 2001	RCT: single-blind; short *vs* long-term PRP	UK/OP	44	Endurance; HRQL CRDQ ($p<0.011$); dyspnoea ($p<0.021$), emotion ($p<0.003$), mastery ($p<0.027$)
Berry *et al.* 2003	RCT: single-blind; short *vs* long-term PRP	United States/OP	140	Physical function and disability; pulmonary function Disability: $p<0.016$ long- *vs* short-term Physical function: increased walk distance ($p< 0.03$ long term); stair climb time ($p< 0.05$) Pulmonary function: NS
Sewell *et al.* 2006	RCT conventional seven-week supervised program (n=50) or to a four-week supervised programme (n=50).		100	At seven-week follow-up, patients in the four-week program attained higher submaximal exercise performance times for a mean difference 124 seconds (p=0.024).

Pulmonary rehabilitation in respiratory conditions other than COPD

Although there are some studies stretching the beneficial role of pulmonary rehabilitation to other respiratory diseases, the reported evidence is highest for COPD.[19]

It is believed that pulmonary rehabilitation has positive effects in a large range of chronic pulmonary conditions including asthma.[20,21] The scientific rationale for providing pulmonary rehabilitation to patients with non-COPD diagnoses is the same as for COPD. As in COPD, persons with other forms of chronic respiratory disease commonly experience deconditioning and exercise intolerance, disabling symptoms of dyspnoea and fatigue, impaired health status and quality of life, systemic inflammation, nutritional impairments, and/or muscle dysfunction (related to deconditioning, loss of fat-free mass, and/or corticosteroid use) that collectively impair functional status along with abnormalities of pulmonary function.[20]

Modification of the relative emphasis on the core programme components and overall programme content may be required to maintain patient safety and to meet individual patient needs and goals which may differ from the standard goals for COPD.[2] Disease-appropriate and age-appropriate tools for the assessment of exercise capacity, health status, and quality of life should be utilised, and efforts must be made to integrate topics relating to non-COPD diagnoses in situations in which the patient group is composed predominantly of COPD patients.

Although most of the studies published to date, which investigate the outcomes of pulmonary rehabilitation for disorders other than COPD are uncontrolled trials or case series, randomized clinical trials are beginning to emerge[22,23] with the strength of existing evidence supporting pulmonary rehabilitation varying across the different diseases.

Importance of nutritional and psychological care

The need of a multidisciplinary programme also includes nutritional and psychological assessment. Nutritional depletion is commonly found in COPD patients and this affects both the respiratory and skeletal muscle function, contributing to an increased morbidity and mortality.[24] Schols and colleagues

found that patients who increased their weight by more than 2 kg had a significantly better survival, independently of their initial body mass index.[25] Because of the morbidity and mortality associated with underweight COPD patients, it is therefore being recommended that interventions should be extended to prevention and early treatment of weight loss, before patients become extremely wasted, and therefore put more emphasis on dietary change than on medically prescribed supplementation.[2,17]

The psychological input is also required as patients with chronic respiratory diseases have an increased risk for anxiety, depression, and other mental health disorders[26,27] leading to frustration with poor health and an inability to participate in activities which can present as irritability, and a hostile attitude toward others. In the later stages of respiratory disease, progressive feelings of hopelessness and inability to cope often occur. When psychologic support is provided within the rehabilitation setting, one will be able to help facilitate the adjustment process by encouraging adaptive thoughts and behaviours as well as helping patients to reduce any negative emotions present.

As is documented in a review of randomized studies, Griffiths and colleagues reported reduced symptoms of anxiety and depression following a 6-week pulmonary rehabilitation program, with symptoms of depression remaining significantly reduced at the 12-month follow-up.[28] Also, Emery and colleagues[29] found reduced anxiety and improved cognitive function following a 10-week pulmonary rehabilitation intervention.

Recommendations and conclusion

With a constant increase in COPD patients, and this disease ranking 4th for mortality and morbidity rates, more research in this field is required to further look into the above discussed issues in order to help the local development of the best pulmonary rehabilitation service for the treatment of respiratory patients. Coordination of services is very important, especially during episodes of exacerbation, which are characterized with high morbidity and a marked increase in use of health care resources.

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Management of inflammatory dentigerous cysts in children: report of two cases

Erica Scerri, Alexander Azzopardi

Abstract

Inflammatory dentigerous cysts are usually associated with a carious or non-vital primary tooth. Consequently they are found in children with a mixed dentition. This report describes two cases of inflammatory dentigerous cysts associated with the lower second premolars. Both cases were treated by marsupialisation of the cysts that eventually led to the spontaneous eruption of the premolars.

Introduction

Odontogenic cysts in children are rare with only 1% of the radicular cysts and 9% of the dentigerous cysts occurring in the first decade of life.[1] Dentigerous cysts are developmental in origin and are usually associated with impacted teeth or teeth that erupt late. Inflammatory dentigerous cysts are associated with the roots of carious or non-vital primary teeth and the crowns of unerupted permanent successors. Consequently, they can only be found in the mixed dentition. A possible pathogenesis of these cysts is periapical inflammation from a non-vital deciduous tooth spreading to involve the follicle of the unerupted permanent successor tooth. The inflammatory exudate causes the reduced enamel epithelium to separate from the enamel leading to the formation of a dentigerous cyst.[2] Several authors[2-4] have reported cases of dentigerous cysts associated with an infected predecessor tooth. The following two case reports show the successful management of two such cases referred from general dental practice.

Keywords

Dentigerous cysts, Children, Inflammatory, Treatment

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Case report 1

A healthy 7-year old boy was referred to the Dental Department of St Luke's Hospital, Malta in May 2005 following extraction of a carious lower right second deciduous molar (85) in General Dental Practice. A hard swelling in the lower right buccal sulcus in the premolar region did not subside even following antibiotics and was still present one week after the extraction. A panoramic radiograph (Figure 1) showed a large unilocular radiolucent lesion surrounding the crown of the lower right second premolar with displacement of the lower right premolar crowns towards the lower border of the mandible. Marsupialisation of the cyst was carried out under local anaesthesia, and a specimen was sent for histological examination. The patient was provided with an acrylic plate with a plug and was instructed to irrigate the cyst cavity with a chlorhexidine mouthwash. The histology report was that of a radicular cyst. The patient was reviewed every month to reduce the depth of the acrylic plug. Radiologic examination showed the cyst to be reducing in size and by August 2005, a panoramic radiograph showed the lower right premolars to be migrating occlusally. In October 2005, the cyst opening had closed completely and it was decided to re-open the cyst cavity. This was carried out under local anaesthesia and cold curing acrylic was used to build-up the plug on the lower plate. Two months later, radiologic examination showed that the cyst cavity was decompressing and the lower right premolars were erupting into position (Figure 2). By January 2007 the lower right premolars were clinically visible and by July 2007 they were fully erupted. The patient is still being reviewed at the orthodontic clinic of Mater Dei Hospital, waiting for the permanent dentition to be established.

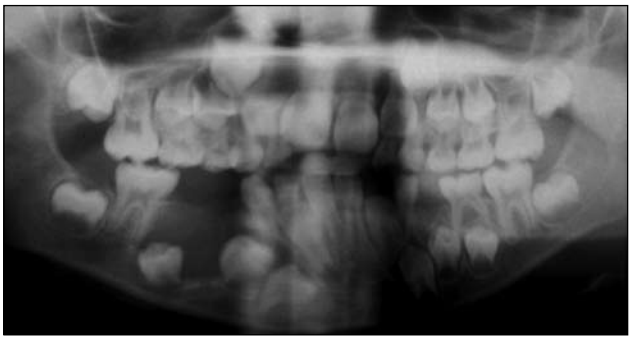

Figure 1: *Inflammatory dentigerous cyst involving the mandibular right second premolar.*

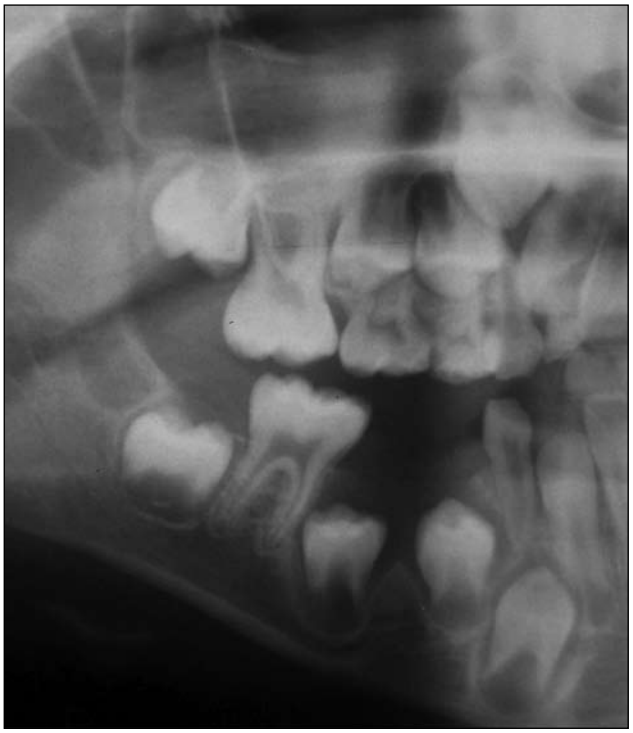

Figure 2: *Inflammatory dentigerous cyst decompressing and lower right premolars erupting into the dental arch.*

Case report 2

In November 2006, a healthy 10-year old boy presented at the Dental Department with a firm swelling associated with a grossly decayed lower left second deciduous molar. The lower left first deciduous molar and the lower right deciduous molars had been previously extracted. A panoramic radiograph (Figure 3) revealed a well defined unilocular radiolucency embedding the crown of the lower left second premolar which was displaced apically. The carious lower left second deciduous molar was extracted and cyst marsupialisation was carried out under general anaesthesia. The cavity was packed with Bipp gauze during the first two weeks post-operation. The patient was then provided with a removable lower space maintainer with an acrylic plug in the cyst region to maintain the opening of the cyst patent. The patient was instructed to rinse with a chlorhexidine mouthwash and was reviewed every two weeks to reduce the height of the plug. The lower left premolars erupted spontaneously as the cyst decompressed. By May 2007 the lower left first premolar had started to erupt and the lower left second premolar was clinically visible by July 2007. The acrylic plug was removed completely but the patient was instructed to keep on wearing the lower space maintainer to prevent mesial tilting of the lower first molars. In April 2008, a panoramic radiograph (Figure 4) showed that the radiolucent lesion in the lower left premolar region had resolved completely. The lower left second premolar was however impacted beneath the contact point of the lower left first molar. The patient also had a developing Class III malocclusion and impacted upper second premolars and was therefore referred for orthodontic treatment. He is still being followed up at the orthodontic clinic of Mater Dei Hospital.

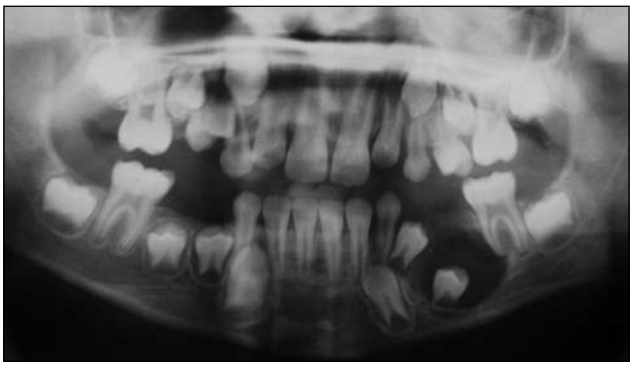

Figure 3: *Cystic lesion involving the lower left second premolar. The roots of the grossly carious lower left second deciduous molar were in contact with the cyst wall.*

Discussion

There have been 20 reported cases of dentigerous cysts in Maltese children in approximately the first decade of life from 1961 till 2006. They are more common in boys and more likely to occur in the lower jaw (unpublished data compiled by Prof. G. E. Camilleri). Both cases described here were associated with the lower second premolar teeth and both patients were males. The radiographic appearance of the cystic lesion in both cases was that of a unilocular, well defined radiolucency enclosing the crown of the second premolar tooth suggesting the diagnosis of a dentigerous cyst. However, since dentigerous cysts are usually associated with impacted teeth or teeth that erupt late, the radiographic signs, in both cases, did not support the diagnosis of a developmental dentigerous cyst. In the first case presented here, there was still no root formation of the second premolar and therefore it was unlikely that tooth eruption had started. In the second case, although root formation had started, there was nothing to suggest that the second premolar might have been impacted. Therefore it was unlikely that the pathogenesis of both cystic lesions was that of a dentigerous cyst which is developmental in origin. On the other hand, there appeared to be a definite correlation between the cystic lesion and periapical pathology from the overlying carious predecessor tooth especially in the second case were the roots of the carious deciduous second molar could be seen touching the cyst wall. This suggested that the cystic lesions were inflammatory dentigerous cysts. A specimen was sent for histological examination in the first case only and although the histopathological report came back as a radicular cyst it is histologically very difficult to distinguish between inflammatory dentigerous cysts and radicular cysts[2] and radicular cysts associated with deciduous teeth are very rare.[5] Unfortunately a specimen was not sent for histology in the second case. Therefore, a diagnosis of the cystic lesion in this case was not possible. However it is worth noting that a biopsy should always be taken to exclude odontogenic tumours and other cystic lesions such as the odontogenic keratocyst. These lesions may present in a similar way but would necessitate more aggressive treatment.

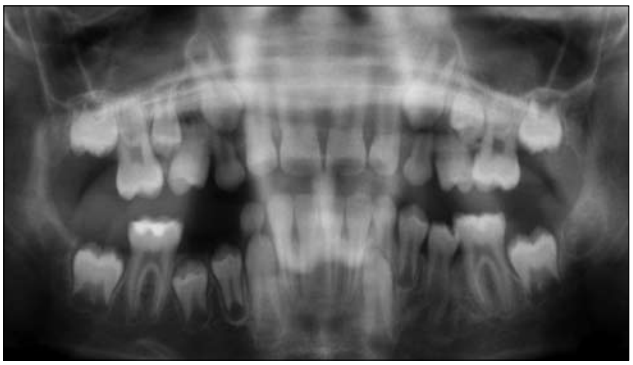

Figure 4: *Lower left first and second premolars fully erupted*

Dentigerous cysts in adults are usually treated by surgical enucleation and extraction of the associated tooth affected by the cyst. In the case of small cysts, enucleation and preservation of the involved tooth is sometimes advocated in younger patients. Larger cysts are initially reduced in size by marsupialization followed by surgical enucleation at a later stage.[6] A more conservative approach has been used in our two cases of inflammatory dentigerous cysts because of the young age of the patients. Following the removal of the carious deciduous teeth, decompression of the cysts was carried out and the opening was then kept patent with the use of an acrylic plug to allow the cyst to shrink and at the same time allow bone regeneration to occur. This eventually resulted in the spontaneous eruption of the premolars in both cases and has prevented the loss of any permanent teeth or damage to any of the adjacent structures.

The above two cases highlight the importance of preventive measures and proper management of carious deciduous teeth to avoid these complications. Regular follow-up of the deciduous dentition is of the utmost importance because an inflammatory dentigerous cyst can attain a considerable size before the patient becomes aware of it, this usually being asymptomatic. Simple management of inflammatory dentigerous cysts usually results in a satisfactory outcome without loss of teeth. The prognosis is much better in children because of the greater eruptive potential of teeth with open apices and the greater regenerative potential of young bone.

Acknowledgements

We would like to thank Professor George Edward Camilleri for providing us with the data of dentigerous cysts in Maltese children.

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Case Report

A rare cause of hypoglycaemia

Robert Sciberras

Abstract

This paper describes a case study concerning a young man on treatment for psychiatric illness who developed severe episodes of hypoglycaemia. After several investigations, lithium therapy was implicated. Stopping this treatment resulted in the patient being relieved of these episodes.

A rare cause of hypoglycaemia

F.A. is a 36 year old male health care worker with a long-standing history of psychiatric illnesses and repeated admissions to the Psychiatric Short-Stay Ward. The depressive illness was precipitated by an accident in a previous work-place. Other past history included hypertension of 4 years duration and spinal surgery for a prolapsed disc in 2006.

The patient is married to a diabetic lady, who is on gliclazide and metformin. She monitors her own blood glucose at home using a glucose meter.

F.A. was referred in October 2008 complaining of recurrent hypoglycamic attacks occurring approximately every 2 days for the past 4 weeks. The low glucose levels ranging between 2.2mmol/L and 2.7mmol/L were documented by his wife using her glucose meter. The hypoglycaemic attacks were typical and included excessive sweating, tremors, nausea and at times, episodes of confusion. The episodes were relieved by the patient ingesting a large bar of chocolate followed by sugary drinks.

Keywords

Psychiatric illness, lithium therapy, hypoglyacemia

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The patient was on clozapine 25mg, ½ tablet three times a day, lithium 400mg tabs, 600mg at night, mianserin 10mg, two tablets three times a day and paroxetine 20mg two tablets in the morning and one tablet in the evening. His blood pressure was well controlled with amlodipine 5mg once daily.

There were no other systemic complaints, and no relevant family history. There was no recent change in appetite or weight. Examination was unremarkable. Given his work-place and also his home situation, surreptitious ingestion of oral hypoglycaemic agents was suspected but subsequently eliminated as the cause for his attacks. At his place of work he did not have access to any hypoglycaemic agents. At home, his wife kept her medications under lock and key particularly because the couple had two small children. She could also account for all her tablets. Psychiatric consultation concerning whether any of the psychiatric medications could be causing hypoglycaemia proved negative. All investigations including thyroid function tests were normal. Serum lithium level was 0.45mmol/L (normal range 0.6-1.2mmol/L). The patients did not present a history of lithium toxicity.

The patient was admitted to Gozo General Hospital for monitoring at the end of October 2008. During admission two hypoglycaemic attacks occurred and were witnessed by the author. The glucose levels were 2.6mmol/L and 2.7mmol/L respectively. The hypoglycaemic attacks had to be aborted rapidly by dextrose infusion as the patient became very symptomatic, confused and on the point of becoming aggressive. Blood tests were taken during the hypoglycaemia: C-Peptide level was 5.85ng/ml (normal range is 0.80-4.00ng/ml), insulin level was 31.0microU/ml (normal range 2.0-25.0microU/ml), and proinsulin level was 88pmol/L (normal range is 6.4-9.4pmol/L). These levels were inappropriately high for a patient with hypoglycaemia.

An insulinoma was suspected and an urgent computerised axial tomography of the abdomen was carried out, including 1.5mm slices at the pancreatic level. This was reported as normal.

Meanwhile hypoglycaemic episodes were still occurring in spite of continuous dextrose infusion and so the patient was started on prednisolone 10mg three times a day. This medication put an end to the hypoglycaemic episodes and the patient was discharged home pending further investigations.

An Indium-111 octreotide scintigraphy was performed on the 17th of December 2008, 4 hours and 24 hours following intravenous administration of 160MBq of Octreoscan. Both whole body and

SPECT images were acquired. There was no abnormal focus of tracer accumulated in the abdomen. Physiological activity was seen in liver, spleen and kidneys with intestinal activity evident at 24 hours. It was therefore concluded that there was no definite evidence of insulinoma. However sensitivity of octreotide scintigraphy is in the range of only 50% (see discussion below). Surgical consultation resulted in the patient being scheduled for exploratory laparotomy which might have included total pancreatectomy. At the eleventh hour the surgery was postponed due to repeated hypoglycaemic episodes. During one of these episodes, blood investigations showed an insulin level of 22microU/ml (reference range 2.0-25.0microU/ml), C-peptide level of 3.64ng/ml (reference range 0.80-4.00ng/ml), and proinsulin level of 30.4pmol/L (reference range 6.4-9.4pmol/L). The patient was started on diazoxide 50mg, four tablets three times a day and discharged home on the 10th of March 2009.

Two days later the patient was admitted urgently to hospital complaining of fever of 102 degrees Fahrenheit, severe muscle aches and pains, shortness of breath and inability to walk due to generalized weakness and stiffness. There was no wheezing or rash. His eosinophil count was normal. The symptoms had started on initiating diazoxide therapy. A reaction to the medication was suspected, the drug withdrawn and all symptoms resolved. At this point, lithium therapy started to be suspected to be causing the hypoglycaemic episodes in this patient. The dose of lithium was reduced to 400mg at night and the patient discharged. The rest of the medication was kept at the same dose throughout the investigative period. Further visits at out-patients revealed that no further episodes of hypoglycaemia were occurring since reduction of lithium therapy, in spite of the steroids being tailed down. Lithium was eventually reduced to 200mg at night and steroids completely stopped on the 27th of April 2009.

On the 15th of May 2009, the patient was admitted to hospital for a prolonged fasting test. He was advised not to eat anything between 4.00 pm and 8.00 am the following morning. He was allowed to drink water only. Blood glucose was monitored every hour. There were no low blood glucose readings. At 8.00 am, a 75g glucose oral drink was administered. Three hours later the patient suffered a symptomatic hypoglycaemic attack with blood glucose falling to 2.5mmo/L. The insulin level checked at this time was 11.0microU/ml (normal range 2.0-25.0microU/ml), C-peptide level was 3.73ng/ml (normal range 0.8-4.00ng/ml) and proinsulin level was 61.7pmol/L (normal range 6.4-9.4pmol/L). At this point, therefore, the patient was not having spontaneous hypoglyaemic episodes but had a late one precipitated by a glucose load. The lithium therapy was eventually tailed off by the end of June 2009.

The prolonged fasting test was repeated on the 23rd of July 2009. Serum lithium level was <0.10mmol/L (normal range 0.6-1.5mmol/L), and this confirmed that the patient had indeed stopped lithium therapy as instructed. During the fast, the patient did not have hypoglycaemic episodes. At 8.00 am, a 75g glucose load was administered and the patient was observed for six hours later and was allowed to drink water only. Contrary to the first prolonged fasting test, the blood glucose estimations every 30 minutes were stable and there were no hypoglycaemic episodes after the glucose load.

The patient is still being seen regularly at the hospital out-patients department. He is well and has had no further problems since. A letter to the Medicine Authority has been sent reporting the adverse effects caused by lithium and diazoxide.

Discussion

Lithium salts are used in the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorders (manic-depressive disorder) and in the prophylaxis of recurrent depression (unipolar illness or unipolar depression). A literature search for the association of lithium therapy with hypoglycaemia did not reveal significant results. Pinelli *et al* reported neonatal hypoglycaemia with maternal lithium therapy, apart from Ebstein's anomaly, cyanosis, rhythm disturbances and thyroid dysfunction.[1] Shah *et al* performed five-hour oral glucose tests (OGTT) in nine patients receiving lithium therapy and in seven control patients.[2] During GTT mean nadir serum glucose was significantly lower in the lithium-treated patients as compared to controls. The study suggested that chronic lithium treatment may be associated with symptomatic and biochemical hypoglycaemia during OGTT due to a rise in serum cortisol but lack of appropriate rise in plasma glucagon concentrations. Other hormonal effects were studied by Grof *et al*.[3] In this study, lithium treatment resulted in a dramatic reduction in prolactin and growth hormone response to insulin hypoglycaemia. The reduced prolactin response to hypoglycaemia was also confirmed by Grof *et al*.[4] However, other studies tend to contradict these findings. In the intact rat, lithium was found to inhibit glucose- and tolbutamide-induced insulin release, which in turn, causes glucose intolerance and prevents tolbutamide-induced hypoglycaemia.[5] The literature describes one report of a patient with lithium toxicity who presented with hypoglycaemia, acneform lesions, hypothyroidism and nephrogenic diabetes insipidus.[6] However the case study presented above was not a case of lithium toxicity as was proved by repeated blood tests.

The first oral glucose tolerance test also suggested a rebound type of hypoglycaemia. This could explain the fact that when the patient presented originally, his eating chocolate bars to alleviate a hypoglycaemic attack was in fact triggering the next one. The levels of pro-insulin were very high (up to 9 times the upper laboratory reference range). Pro-insulin has weak insulin-like biological activity of its own right, but a much longer half-life than insulin. It might therefore have contributed to a reactive-type of hypoglycaemic reactions. A diagnostic problem which was encountered was the fact that the octreotide scan is not always helpful, since the false negative rate could reach up to 50% due to different types of somatostatin receptors present in this tumour type.[7,8,9]

The duration of the prolonged fasting tests might not be the recommended one, however in this case it served its purpose since the difference between the 2 tests occurred after the glucose challenge; when the patient was on lithium there was

severe hypoglycaemia and while off lithium the patient did not suffer any adverse events. So the two scenarios were directly comparable. Furthermore, stopping lithium therapy has resulted in the total absence of further hypoglycaemic episodes to date, virtually ruling out insulinomas since no definite treatment for these tumours was undertaken. Furthermore the patient has not developed other conditions e.g. diabetes mellitus.

It is clear that further studies need to be carried out in order to investigate the role of lithium in causing hypoglycaemia. However any patient on lithium suffering from recurrent episodes of hypoglycaemia may need a review of psychiatric treatment.

Acknowledgements

The author acknowledges the input of Dr. Mario Cachia in suggesting that lithium therapy could cause hypoglycaemic episodes.

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Donation of a clinical-skills simulation model by Bayer-Schering Pharma

The Department of Obstetrics and Gynaecology within the Faculty of Medicine and Surgery has been the recipient of a simulation model aimed at assisting the development of clinical skills by medical students. The Zoe® Gynaecologic Simulator was kindly donated by Mr. Simon Delicata who is the local representative of the international-based company Bayer-Schering Pharma. The model consists of a full-sized adult female lower torso designed as a training tool developed to assist health professionals to teach the processes and skills required to perform certain gynaecological procedures.

Bayer Schering Pharma AG is an international healthcare company that is committed to sustainable development in various fields of healthcare including gynaecology. The present donation is a clear example of the commitment being shown by the company of the positive inter-relationship between industry and academia. The company has strongly supported the Department of Obstetrics and Gynaecology throughout the last years. It has set up the annual Bayer-Schering Pharma Prize in Obstetrics & Gynaecology that is awarded to the student who obtains the highest aggregate mark in the speciality during the final examinations of the Medicine and Surgery course. In addition, the company has sponsored publications on the history of midwifery education and on the history of gynaecology in Malta prepared by the Department. The present gift is a welcome addition to the educational tools armamentarium of the Faculty since it helps augment the clinical skills simulation laboratories being set up by the Faculty.

Implementation of a graft surveillance programme for infrainuginal vascular bypass surgery

Noel Cassar, Branko Dunjic, Kevin Cassar

Abstract

Aim: Patients undergoing bypass graft placement in the lower limb are often entered into a graft surveillance programme using duplex scanning. The aim of this programme is to identify stenoses in vein grafts before they become symptomatic and treat these by angioplasty or surgery, thus prolonging the patency of the graft. This paper aims at reporting on the progress and viability of this programme at Mater Dei Hospital, Malta.

Method: Infrainguinal bypass grafts carried out between July 2007 and May 2009 were enrolled. Scanning starts during the patient's in-hospital stay at one week post-operation. It is then scheduled at 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, and yearly afterwards. When a significant stenosis is encountered, the patient is referred for angioplasty. Surgery would be considered in cases when angioplasty is not an option.

Results: During this period 56 patients were recruited. At one week post-op the patency rate was 100%. At 6 months the primary unassisted patency was 77.5% while the primary assisted patency was 87.5%. At 12 months the primary unassisted patency was 50% while the primary assisted patency was 77%. Secondary patency rates at 6 and 12 months were 95% and 82% respectively.

Conclusion: The graft surveillance programme ensures that any problem detected in the post-operative period is dealt with as soon as possible. The study shows that this programme is being effective in that assisted rates (i.e. after angioplasty or surgery) are better than unassisted rates.

Keywords

peripheral vascular disease, ischaemia, angioplasty, duplex Doppler ultrasonography

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Introduction

For patients with severe peripheral vascular disease, especially those with long occlusions of the superficial femoral and popliteal arteries, infrainguinal vascular bypass surgery may be the only option for revascularization of the limb.[1-4] There are three main types of infrainguinal bypass surgery – femoro to above knee popliteal bypass, femoro to below knee popliteal bypass and femoro to distal bypass. The latter can be femoro to anterior tibial, femoro to posterior tibial or femoro to peroneal bypass. Once patients have been scheduled for a bypass procedure they are assessed medically to check whether they are fit for the operation and they are scanned by the vascular surgeon in charge to look for any suitable vein graft which can be used as a new conduit. Vein grafts are preferred over PTFE grafts as they have longer patency than the latter. Patients who undergo such operations are not simply discharged once they have recovered from their operation, but are followed up on a regular basis to check the progress of their graft and therefore of their clinical condition.

This is in accordance with the recommendations of The Trans-Atlantic Inter-Society Consensus on the Management of Peripheral Arterial Disease (TASC), which states that patients "who undergo bypass graft placement in the lower extremity for the treatment of claudication or limb-threatening ischaemia should be entered into a clinical surveillance program." [1] This consists of asking the patients how they are doing in regards to their previous symptoms and whether any new symptoms have developed since the operation. Vascular examination of the lower limb should take place as well with palpation of inflow, graft and outflow vessel pulses. Resting and post-exercise Ankle brachial pressure indices (ABPI) should be measured as well.

Although strictly not a TASC recommendation, as ongoing trials are still needed to determine its efficacy, many surgeons also enter their patients into a graft surveillance programme whereby the graft is scanned by duplex ultrasound at regular intervals. The aim of this scanning is to check that the graft is working and to detect and treat any stenosis in the graft. This article reports on the setting up of such a graft surveillance programme in Malta.

Methods

Once a patient undergoes a vascular bypass operation he or she spends a day in an ITU/HDU setting and is then transferred to a normal surgical ward. The patient is seen daily to monitor his or her progress and at one week post-op the first graft scanning takes place. The scanning needs to answer two main questions:

- Is the graft working?
- Is there any stenosis?

Duplex ultrasound Doppler is used to answer these questions, by means of waveform analysis and peak systolic velocities measurement. Colour Doppler is used to detect blood flow (Figures 1 and 2).[5-6]

In terms of waveform analysis, triphasic waveforms represent better blood flow than biphasic which are in turn better than monophasic waveforms.

Blood flow is assessed in the artery proximal to the graft, the graft itself and the outflow artery. An increase in Peak Systolic Velocity of more than 3 times along the vessel is considered significant and is suggestive of a stenosis (Figure 3).[5-6] Peak systolic velocities of less than 20cm/sec indicate that the flow through that segment of graft is poor and may require intervention.[7]

Stenosis may occur at any site along the graft including the proximal and distal anastomosis.

If during this process any stenosis is identified the patient can then be sent for angioplasty of the stenosis. This ideally should happen before such a stenosis becomes clinically significant. Sometimes graft scanning will reveal long occlusions which are not amenable to angioplasties. In such cases, if possible, the patient will be offered redo bypass surgery.

Scanning takes place at one week post-op, then continues at 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months and yearly afterwards. Only patients who underwent bypasses using vein grafts are scanned. PTFE grafts are not routinely scanned as they cannot be angioplastied should the need arise.

This report covers graft scanning done for those infrainguinal bypasses carried out between August 2007 and May 2009 at St Luke's Hospital and Mater Dei Hospital by the firm of one of the authors (KC).

Records for primary unassisted patency, primary assisted patency, and secondary patency were kept. Primary unassisted patency refers to patency of the graft without any intervention. Primary assisted patency refers to patency of the graft with the help of angioplasties when stenosis occurs, whilst secondary patency refers to those cases where the graft is occluded and needs surgical intervention (redo bypass) to revascularise the limb.

Results

Our study period was over 22 months (from August 2007 to May 2009). During this period sixty infrainguinal vascular bypasses were done. These patients entered the study at different times; therefore not all of them had the same number of scans post-op. Those patients who were operated near the end of the study period, had only a few number of scans.

Post-operatively at 1 week all the grafts were patent. Out of the 60 patients, 56 made it to the first scan at one week post op and these were all patent.

At 6 weeks, 49 patients were scanned and 46 grafts were patent (94%). One of the other patients had successful redo vascular bypass surgery bringing the secondary patency rate to 96%.

At 3 months, 44 patients had their grafts scanned and 40 patients had patent grafts (90%). Another patient needed redo surgery and this brings the secondary patency rate up to 95%.

At 6 months 31 out of the 40 patients scanned had their grafts patent (77.5%). Four other patients had successful angioplasty bringing the primary assisted patency to 87.5%. Secondary patency was 95% (38 out of 40 patients).

At 12 months 22 patients were scanned. At this point primary unassisted patency was 50%, i.e. only 11 patients had their graft patent. Primary assisted patency was much better at 77%, with another 6 patients having angioplasties. Secondary patency was slightly better at 82% (18 patients out of 22).

At 18 months only nine patients were scanned. Four of these grafts were patent – 44% primary unassisted patency, while another patient had an angioplasty, thus putting the primary assisted patency at 56%. Another patient had redo-surgery with the secondary patency rate thus being 67%.

The above information is shown in Table 1 and in the Kaplan-Meier curves (Figure 4) for the various patencies described above. The primary end-point is sonographically detected graft stenosis.

Discussion

As we can see from the figures in the table below, primary assisted patency and secondary patency were significantly better

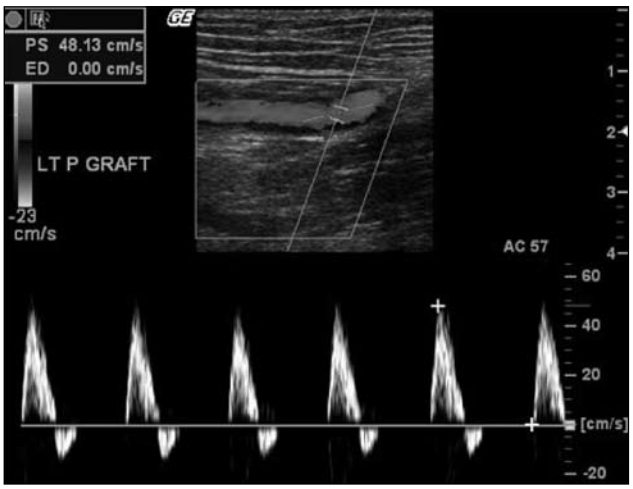

Figure 1: *Good blood flow on Colour Doppler of a Saphenous Vein graft and biphasic waves on duplex ultrasound*

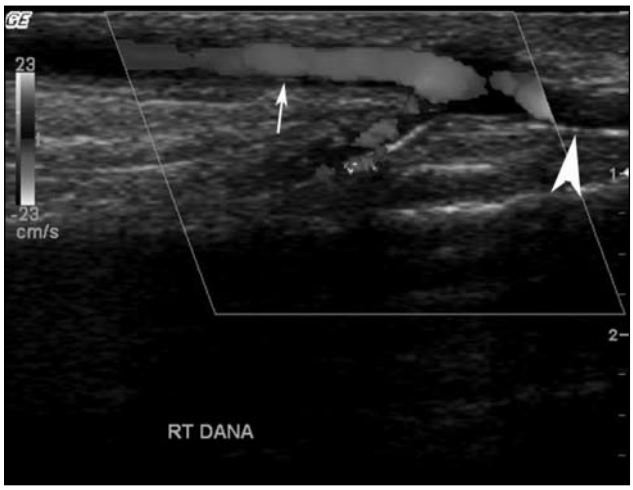

Figure 2: *Distal anastomosis of an in-situ bypass graft. The size of the graft (arrow) matches the diameter of the tibial artery (arrowhead)*

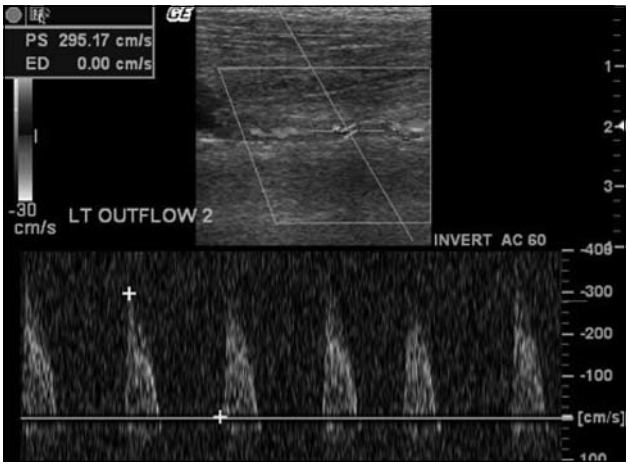

Figure 3: *Peak systolic velocities are elevated (295 cm/sec) at the point of abnormal color Doppler signals. This indicates a focal stenosis of 50 to 75% in the native artery distal to the graft.*

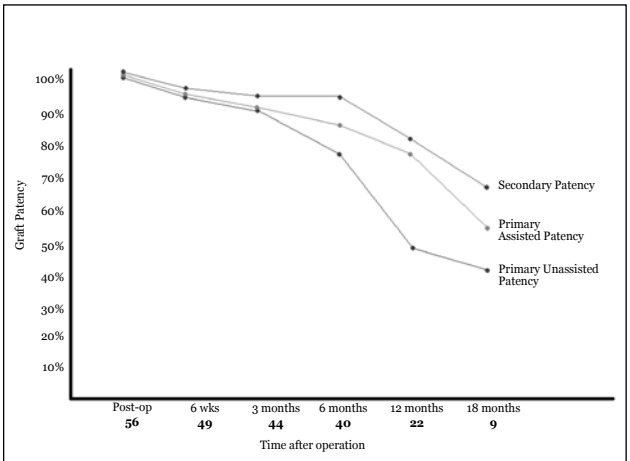

Figure 4: *Kaplan-Meier Curves for primary unassisted, primary assisted, and secondary patency rates. Figures below "time after operation" denote the number of patients at that stage*

Table 1: *Primary unassisted patency, primary assisted patency and secondary patency for infrainguinal bypass grafts at different post-operative duplex scanning*

Time post-op	Number of patients	Primary Unassisted Patency	Primary Assisted Patency	Secondary Patency
One week	56	56 (100%)		
6 weeks	49	46 (94%)	46 (94%)	47 (96%)
3 months	44	40 (91%)	40 (91%)	42 (95%)
6 months	40	31 (77.5%)	35 (87.5%)	38 (95%)
12 months	22	11 (50%)	17 (77%)	18 (82%)
18 months	9	4 (44%)	5 (56%)	6 (67%)

than primary unassisted patency from the sixth month onwards. This indicates that the graft surveillance programme, which aims at treating significant stenoses or occlusions as soon as possible by sending them to angioplasty or surgery if necessary, is being efficient at detecting those patients who need further treatment. Were it not for the surveillance programme these patient might present at a later stage where treatment would be more complex, if at all possible. This is in keeping with several other studies which also mentioned the importance of graft surveillance by duplex ultrasound. [8-10]

Conclusion

This study shows that a graft surveillance programme makes a lot of sense in the setting of infrainguinal bypass surgery and we look forward to official recommendations by TASC on this matter.

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The nurse of the Mediterranean

Saviour Pisani

During the First World War Malta did not take an active part in the fighting. Britain was joined in an 'entente' a friendship agreement with France since 1904 and later with Russia in 1907. On the other hand Germany was allied to the Austrian-Hungerian Empire, hence when the Great War started in July 1914 there were France, Britain and Russia on one side and Germany and Austria-Hungary on the other. The British fleet "ruled the waves", hence with France and Britain as allies, to be joined later by Italy, the Mediterranean was more or less an allied lake, with Malta in the centre.

During the nineteenth century the Ottoman Empire was falling apart, and one of the big problems that faced the foreign office of Britain in the nineteenth century was the Ottoman Empire known as the sick man of Europe. Russia was looking at it from the part of the chief inhibitor of its demise, while Britain was taking the role of a doctor. Russia is a vast country, stretching from the Baltic to the Pacific and from the Arctic to the Black Sea. Its biggest problem was that it could not use its ports throughout the whole year. Its arctic port, the Archangel, was blocked by ice; its Baltic ports had a similar problem in winter. Furthermore the Baltic Sea was dominated by the German navy in XXXII. The latter was secondary to that of Britain. Russia's far eastern ports – Vladivostostock – was also frozen and far too distant. The Black Sea ports were closed by the Ottoman Empire during hostilities. The Russian ships had to pass through the Dardanelles to reach the Mediterranean and if the Dardanelles were under a hostile power no merchant ship could pass – i.e. the Russian navy was bottled up in the Black Sea.

Keywords
nurse, Mediterranean, first world war, Rupert Brooke

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The British were always suspicious of the Russian intentions towards the Ottoman Empire, and the Crimean War of 1854 was fought by Britain, France and the Ottoman Empire against Russia to destroy its main base of Sevastapol and its fleet. By the treaty of San Stefano and the convention of Berlin blocked by Bismarck, the small Balkan states of Bulgaria, Serbia, Rumania and Montenegro appeared and these showed that they were very jealous of their independence and were far more efficient than the decadent Ottoman Empire to thwart Russian ambitions to enter the Mediterranean Sea. Still the Balkans was not so stable and in 1911-1912 the Balkan Wars erupted. In 1914 after the Archduke Ferdinand was assassinated in Sarajevo, Austria-Hungary declared war on Serbia and the First World War started. The Ottoman Empire had a friendly relationship with Germany, its military was trained by Prussian officers and when the battle cruisers – Goeben and Breslan – were caught in the Mediterranean in July 1914 and sailed on to Constantinople where they were given as a present to the Sultan, the Ottoman Empire found itself on the German side together, incidentally with Bulgaria which felt short-changed by Serbia.

The First World War started in high spirits by both sides. However, it soon degenerated in trench warfare. The British old professional army, known as the old contemptible was soon decimated and new regiments came from Britain and its empire to replace the heavy losses. The French also lost many soldiers when they moved on Alsace and Lorraine, lost in 1870. The Russians lost thousands and thousands of soldiers in the battle of Tannenberg. Their equipment was found most wanting and it was clear to all military chiefs that Russia could not sustain a war of attrition. The soldiers went into battle without rifles, they had to pick rifles from dead or wounded colleagues as they advanced along the front. The Russian army needed munitions, heavy guns, transport, rifles and all that a modern war entails. The French knew that if the Russian front were to collapse – as it did later in the war, the full fury of the German army would be let loose on them. The only way available to supply them was by sea. The Baltic Sea was dominated by the German fleet, while the Archangel was hardly practical. Hence Winston Churchill, who was lord of the Admirality at that time, thought of supplying the Russian army from its Black Sea ports. To do this he had to open the Dardanelles to allied shipping, which really meant he had to knock the Ottoman empire out of the war. This he deemed a not so difficult task - after all the Ottoman Empire had been falling apart for more than a century, and it was kept in one piece thanks to the efforts of the British Government, the

chief interventionist being Disraeli.

Possibilities were very good. With Constantinople in British and French hands, the Russian army could be supplied. The Czar government secure from its internal enemies - the Bolshevists – could initiate a new Russian offensive in the East, thus relieving the Western Front from pressure.

Churchill thought that the Dardanelles could be forced by the navy alone. In conjunction with the French, the British sent the pre-dreadnaughts. This led to a major disaster, the Turkish waters were infested with mines and the approaches with heavy fortified forts. The allies lost a number of battleships through enemy activity and German submarines were reputed to be in the area. Hence it was thought that the Gallipoli Peninsula should be cleared of the hostile troops by landing troops on it – the Anzacs, Austrialian and New Zeland troops who were in Egypt at that time. However, the element of surprise had been lost and when the troops finally landed they found the Turkish troops ready for them. No real progress was done and after a few months, in which thousands of Allied troops were either killed or wounded, they were evacuated from the Gallipoli beaches, Winston Churchill resigned and eventually the Czar regime collapsed. Luckily the United States came into war on the side of the allies and the Western front was saved.

Malta was warned to get itself prepared to receive the wounded of the Gallipoli campaign. The Governor at that time was Lord Melhuen who was a very good organiser. Plans were immediately started to turn Malta into a giant hospital. At that time there were four hospitals in Malta, the Central Hospital for civilians, the Blue Sisters' hospital for merchant seamen, Bighi hospital for the navy and Mtarfa Hospital for the army. Their total capacity was about three hundred beds, if all the rooms and available space were utilized there would be five hundred beds – far short of what was necessary. The Holy Infirmary at Valletta was roped into service. Some new schools were turned into hospitals and barracks which had been vacated by the troops turned into hospitals. Originally Allied command in Egypt asked for 3000 beds. However, with mounting injuries it was soon found that that extimate was not nearly enough and more bed space was created. A hospital is totally useless without adequate staff, doctors, nurses, attendants, labourers, technicians, cooks, laundry people, etc., etc.

The soldiers invaded the Gallipoli Peninsula on the 25th April 1915. Many soldiers were wounded or killed. Up to the end of May 1915, 38,000 soldiers were either killed or wounded. These figures will make us understand the extent of the problem facing the authorities over here. The first wounded reached Malta on the 4th May 1915. They were carried on hospital ships, painted white with a big red cross painted on their sides. When the people realized that the wounded of Gallipoli were entering the bastions, the mood was very sombre. The harbour had the aspect of a sick ward in a general hospital, silence all around.

One thousand two hundred solders, wounded from the front were brought on that day. Barges went against the hospital ships and the injured soldiers were brought down very gently by the cranes on stretchers and from the barges onto the shore. From the quay they were taken to the Holy Infirmary at Valletta where they were examined by top British and Maltese doctors, from there they were sent to other centres according to their injuries. A Maltese doctor appointed by the Governor himself for such duties was Dr Robert Randon who was placed in charge of Fort Tigne, now turned into a hospital of about 1,000 beds.

The processes of wounded soldiers on stretchers drawn by mules and horses passed through Kingsway, now Republic street, in Valletta on its way to the Holy Infirmary. It was described as that of Good Friday, silence reigned and people on each side on the pavements welcomed the soldiers with cigarettes, sweets, flowers and chocolate. The wounded soldiers most of them very young showed their appreciation by waving to the people and from that day the close bond between Malta and Australia was born. Indeed a lot of these soldiers died in Malta and they were buried at Braxia Cemetery at Pietà near where the football club now stands.

May I be permitted here to read Rupert Brooke poem The Soldier written in that period of time.

If I should die, think only this of me
That there in a corner of a foreign field
That is forever England. There shall be
In that rich earth a richer dust concealed.
A dust whom England bore, shaped, made aware
Gave, once, her flowers to love, her ways to name,
A body of England's , breathing English air,
Washed by the XX, blast by suns of home.

Perhaps if we were to substitute Australia for England here, we can better understand the atmosphere, the sorrow and anguish that reigned in Malta that summer of 1915.

Up till the end of May, 4000 wounded had arrived and they were bring treated in 8 hospitals. By September, 10,000 wounded had arrived. By March 1916, there were 20,000 hospital beds, in all 80,000 soldiers were treated in Malta. A percentage of them found their grave in Malta. Military funerals were the order of the day, sometimes with eight or more dead soldiers buried on the same day. Since these funerals were having a depressing effect on the general population, it was decided to conduct them from outside the limits of Floriana, from Portes des Bombes to Braxia cemetery.

The Gardens of Argotti, the Mall, and the streets of Valletta were all full of wounded soldiers. Some of them had an amputated arm pushing at colleague in a wheelchair with amputated legs. Some had bandaged heads, others were blind. However, they were cheerful and made friends with the Maltese people who opened the doors of their homes and hearts to them. Ladies organised tea parties and concerts for them. They started to sponsor children by giving them cards found in cigarette boxes. In general the soldiers who survived the Gallipoli experience were quite happy for things could have been far worse for them. In all they were treated in 27 military hospitals, one of them being the newly built school of Sliema. Archbishop Caruana was asked to tell the parish priests not to

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Rare: Angioedema. Laboratory values: decrease in haemoglobin and haematocrit, increase in serum potassium. Frequency not known: peripheral oedema. **For the hydrochlorothiazide component**, other reported adverse reactions include: Aplastic anaemia, bone marrow depression, neutropenia/agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia, depression, sleep disturbances, restlessness, light-headedness, vertigo, paraesthesia, dizziness, transient blurred vision, xanthopsia, cardiac arrhythmias, postural hypotension, respiratory distress (including pneumonitis and pulmonary oedema), pancreatitis, anorexia, diarrhoea, constipation, gastric irritation, sialadenitis, loss of appetite, jaundice (intrahepatic cholestatic jaundice), anaphylactic reactions, toxic epidermal necrolysis, necrotising angiitis, (vasculitis, cutaneous vasculitis), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, photosensitivity reactions, rash, urticaria, weakness, muscle spasm, interstitial nephritis, renal dysfunction, fever. 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NOVARTIS

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ring the bells to let the patients rest. The Archbishop obliged and the bells stopped ringing.

Ghajn Tuffieha was tunred into a giant camp for convalescent soldiers. In all there were 4,000 beds under tents. Three hundred civilian and military doctors were employed. Some top British surgeons came to Malta, like Balance and Garrod, and 1000 British nurses came from the UK.

Gradually things started to calm down. It was obvious that the Allies were making no headway in Gallipoli and they were pushed back. However, on the 25th December 1915 the British and the French landed in Salonika to help the Serbians. The First World War started from Serbia. In the Balkan wars of 1911 and 1912, Bulgaria was offered Macedonia but its share went to Greece and Serbia. Hence Serbia was attacked by Bulgaria, and the British and French went to help. This time the Maltese makeshift hospitals were filled with malaria and typhoid. It is interesting to note that the first cardiac operation was done in Malta on a soldier who had been shot by a Bulgarian sniper.

As the Gallipoli and Salonika campaigns subsided so did the Maltese hospitals empty, to fill again by the Spanish Influenza victims. Employment during the war and when the war finished there was massive unemployment in Malta. A lot of ships had been sunk, food was scarce and hard to get, there was massive inflation and the safety valve of emigration non-existent since Australia had problems of its own. With political aspirations on the increase, the unemployed workers looked at the political leaders like Sir Filippo Sciberras and the next scene was the Sette Gungio rites of 1919.

When the First World War was nearly over the so-called Spanish Flu appeared. The pandemic killed more people than the war itself, although one can attribute it to the war itself. When there is mass movement of troops and civilians with the most basic requisites of hygiene ignored and non-existent, one can expect epidemics. In WW1 Spain was neutral and the first reported cases came from Spain since the censorship of the media was free. It appeared in the US where young people were being called for service in Europe by Widrow Witson, thousands died in their training camps. It infected the allied army in Northern France where a depot was located and then spread to the German army. In all there were three waves of this pandemic and it was characterized by fever, breathing problems, haemoptysis and cyanosis. Hence our hospitals started to fill again on the 4th October 1918. The Government issued regulations to prevent the spread of the disease – avoiding overcrowding and general cleanliness. Between the 1st September 1918 and 1st March 1919 there were 651 deaths. March was the high point of the third wave. The Influenza continued onto 1920. In February and March 656 cases were reported with a mortality of over 30%. The total mortality of the 1918 – 1919 pandemic in Malta was 3 per 1000 of the population.

On the 10th December 1917 His Excellency the Governer declared at the beginning of the session of the Council of Government. "I also desire to record my grateful recognition of the sympathetic hospitality which the people of Malta and Gozo have extend to the sick and wounded that have been brought during the war, of the support that they have given to the British Red Cross and the Order of St John of Jerusalem and the other charitable institutions that have been formed." This was not the first time that Malta took the role of a Nurse in Wartime and it is said that Malta had added a bright chapter to human history and the severance to its hospitals ever be named; for their sacrifice has once more been enthroned, and unselfishness, garbed in nurses' cape or surgoens' uniform, proclaimed the triumph of love.

Professional medical journal publications in Malta

Charles Savona Ventura

Abstract

After the establishment of freedom of the press in 1839, the Maltese medical community initiated the publication of a medical journal in their efforts to maintain professional standards through continuing medical education. The first initiatives unfortunately were often relatively short-lived due to a number of factors. These initiatives were often undertaken by individuals and were often dependant on paid subscription for their maintenance. Longer lasting publications required a change in management policies. The second half of the twentieth century saw the first long-lasting initiative being undertaken by the medical student association; this journal's financial support being dependant on income from advertisements. Twenty years later, the Faculty of Medicine and Surgery initiated a professional journal. These two journals have since changed their name and editorial policies but are still extant in the current publications *Murmur* and the *Malta Medical Journal*.

Keywords

Medical history, medical journals, Malta

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The governments occupying the Maltese Islands had always been on their guard against any form of sedition that could ferment dissent against their governance. This policy required a strict control of locally published material of any form. The French occupation and the subsequent insurrection had however deeply instilled the concept of freedom, including freedom of speech. In the early decades of the 19th century, the Maltese political movement Comitato Generale Maltese under the leadership of George Mitrovich and Camillo Sciberras started pressurising the British Government for a more liberal governance constitution. This political pressure saw the setting up of the 1836 Austin-Lewis Commission that, among other things, was favourable to the introduction of freedom of the press provided that the public interest and loyalty to the British Crown was preserved. By 1838, even before the formal legal withdrawal of press censorship through Ordinance IV published 22nd March 1839, two newspapers - *Lo Spettatore Imparziale* and *Il Portafoglio Maltese* - initiated publication. The eventual publication of the ordinance saw a sudden proliferation of newspapers such as *The Harlequin*, and *Il Mediterraneo - Gazzetta di Malta*.[1]

The withdrawal of press censorship was quickly availed of by the medical community in Malta. In the last quarter of 1838, before the formal withdrawal of press censorship, Dr. C.G. Schinas issued *L'Ape Melitensis - Giornale di Medicina* with the aim of compiling a journal that appealed to both new graduates and the more experienced professional. The journal served to review contemporary medical literature with material being written in the Italian language by the editor himself. *L'Ape Melitensis* ran for only four issues through September to December 1838, the whole volume amounting to 288 pages. Besides the reviews, the journal also include seven original articles that dealt with the 1837 cholera epidemic, Werlhoff's purpura, smallpox vaccination, the pharmacology of *Segala Cornuta*, the use of calomel in intestinal disorders, animal magnetism, phrenology and a description of an improved urinary catheter designed by Dr. Giuseppe Stilon.[2]

The initiative for establishing a medical journal was again taken up on the 1st January 1841 by Dr. C. G. Schinas together with the assistance of the doctors on the staff of the Civil, Ta' Sawra and Santo Spirito Hospitals. This editorial board undertook the publication of a new journal entitled *Il Filocano - Giornale Medico Scientifico e di Educazione* circulated to subscribers against payment [annual subscription: 2s0d]. Initially published monthly, it soon increased its publication frequency to fortnightly. This journal had a wider remit than the previous medical publication, and served as a medium for local and foreign practitioners to publish their views and observations including case descriptions. Its articles included discussions on smallpox and its prophylaxis, and the management of conditions such as tetanus, puerperal sepsis, and mental disease. *Il Filocano* was first issued in January 1841 and was eventually published fortnightly. It ceased publication in December 1842 after

Help Protect Your Patients From Osteoporotic Fractures

NEW With 5,600 IU of Vitamin D!

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alendronate/colecalciferol

The Only Osteoporosis Therapy That Provides

- **Demonstrated Fracture Prevention at the Hip and Spine Plus 5,600 IU of Vitamin D**
- **In a Single, Once-Weekly Tablet**

Actual size

FOSAVANCE™ is indicated for treatment of postmenopausal osteoporosis in patients who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency. FOSAVANCE reduces the risk of vertebral and hip fractures.[1]

FOSAMAX™ and FOSAVANCE are contraindicated in patients with esophageal abnormalities which delay esophageal emptying (eg, stricture or achalasia) and in patients unable to stand or sit upright for at least 30 minutes. FOSAMAX and FOSAVANCE are contraindicated in patients with hypocalcemia (see WARNINGS AND PRECAUTIONS) and in patients with hypersensitivity to any component of these products. Hypersensitivity reactions including urticaria and angioedema have been reported. FOSAMAX and FOSAVANCE, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.[1]

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping treatment.[1]

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates.[1]

NOF = National Osteoporosis Foundation.

References

1. Worldwide Product Circular for FOSAVANCE, 2007.

2. NOF Scientific Statement. National Osteoporosis Foundation's Updated Recommendations for Calcium and Vitamin D_3 Intake. Revised. www.nof.org/prevention/calcium_and_Vitamin D.htm. Accessed 30 July 2009.

Before prescribing, please read the full Prescribing Information on the adjacent page.

Updated NOF guidelines recommend 800–1,000 IU of vitamin D per day for adults ≥50 years[2]

FOSAVANCE 5600 retail price (Pack of 4) € 37,55

MSD MUSCULOSKELETAL

7-11 FSP-2007-W-1224165-J
31-Jul-2011 FSP-2010-MEA-1982-J

1. NAME OF THE MEDICINAL PRODUCT
FOSAVANCE™ 70 mg/5600 IU tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 70 mg alendronic acid as alendronate sodium trihydrate and 140 micrograms (5600 IU) colecalciferol (vitamin D_3).

Excipients:
Each tablet contains 63 mg lactose anhydrous and 16 mg sucrose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.

Modified rectangle-shaped, white to off-white tablets, marked with an outline of a bone image on one side, and '270' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of postmenopausal osteoporosis in patients who are not receiving vitamin D supplementation and are at risk of vitamin D insufficiency.
FOSAVANCE reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration
The recommended dosage is one FOSAVANCE tablet once weekly.
Due to the nature of the disease process in osteoporosis, FOSAVANCE is intended for long-term use.

To permit adequate absorption of alendronate:
FOSAVANCE must be taken with water only (**not** mineral water) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5).

The following instructions should be followed exactly in order to minimize the risk of oesophageal irritation and related adverse reactions (see section 4.4):
FOSAVANCE should only be swallowed after getting up for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).

Patients should only swallow FOSAVANCE whole. Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.

Patients should not lie down for at least 30 minutes after taking FOSAVANCE.
FOSAVANCE should not be taken at bedtime or before arising for the day.
Patients should receive supplemental calcium if intake from diet is inadequate (see section 4.4). The equivalence of intake of 5600 IU of vitamin D_3 weekly in FOSAVANCE to daily dosing of vitamin D 800 IU has not been studied.

Use in the elderly:
In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. Therefore no dosage adjustment is necessary for the elderly.

Use in renal impairment:
No dosage adjustment is necessary for patients with a glomerular filtration rate (GFR) greater than 35 ml/min. FOSAVANCE is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children and adolescents:
FOSAVANCE has not been studied in children and adolescents and therefore should not be given to them.

4.3 Contraindications
Hypersensitivity to the active substances or to any of the excipients.

Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.

Inability to stand or sit upright for at least 30 minutes.
Hypocalcaemia.

4.4 Special warnings and precautions for use
Alendronate
Alendronate can cause local irritation of the upper gastrointestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastrointestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty (see section 4.3). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain or new or worsening heartburn (see section 4.8).

The risk of severe oesophageal adverse reactions appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and are understood by the patient (see section 4.2). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.
While no increased risk was observed in extensive clinical trials with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some of which were severe and with complications (see section 4.8).

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer who are receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, periodontal disease).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (time to onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures was also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending evaluation of the patient, based on an individual benefit risk assessment.

Patients should be instructed that if they miss a dose of FOSAVANCE they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

FOSAVANCE is not recommended for patients with renal impairment where GFR is less than 35 ml/min (see section 4.2).

Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.

Hypocalcaemia must be corrected before initiating therapy with FOSAVANCE (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting FOSAVANCE. The content of vitamin D in FOSAVANCE is not suitable for correction of vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with FOSAVANCE.

Due to the positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption) (see section 4.8).

Colecalciferol
Vitamin D_3 may increase the magnitude of hypercalcaemia and/or hypercalciuria when administered to patients with disease associated with unregulated overproduction of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

Patients with malabsorption may not adequately absorb vitamin D_3.

Excipients
This medicinal product contains lactose and sucrose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Alendronate
If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see sections 4.2 and 5.2).

No other clinically significant interactions with medicinal products are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse reactions attributable to their concomitant use were identified.

Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

Although specific interaction studies were not performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of interactions of clinical relevance.

Colecalciferol
Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D. Anticonvulsants, cimetidine and thiazides may increase the catabolism of vitamin D. Additional vitamin D supplements may be considered on an individual basis.

4.6 Pregnancy and lactation
FOSAVANCE is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.

There are no adequate data from the use of FOSAVANCE in pregnant women. Animal studies with alendronate do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D (see section 5.3).

It is not known whether alendronate is excreted into human breast milk. Colecalciferol and some of its active metabolites pass into breast milk.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

However, certain adverse reactions that have been reported with FOSAVANCE may affect some patients' ability to drive or operate machinery. Individual responses to FOSAVANCE may vary (see section 4.8).

4.8 Undesirable effects
The following adverse reactions have been reported during clinical studies and/or post-marketing use with alendronate.

No additional adverse reactions have been identified for FOSAVANCE. [*Common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000)*]

Nervous system disorders: *Common:* headache ***Eye disorders:*** *Rare:* uveitis, scleritis, episcleritis ***Gastrointestinal disorders:*** *Common:* abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
Uncommon: nausea, vomiting, gastritis, oesophagitis*,oesophageal erosions*, melena
Rare: oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding)(see section 4.4). *See sections 4.2 and 4.4

Skin and subcutaneous tissue disorders: *Uncommon:* rash, pruritus, erythema, *rare:* rash with photosensitivity
Very rare: severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders: *Common:* musculoskeletal (bone, muscle or joint) pain
Rare: severe musculoskeletal (bone, muscle or joint) pain (see section 4.4)
Metabolism and nutrition disorders: *Rare:* symptomatic hypocalcaemia, often in association with predisposing conditions. (see section 4.4)
General disorders and administration site conditions: *Rare:* transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment.
Immune system disorders: *Rare:* hypersensitivity reactions including urticaria and angioedema

During post-marketing experience the following reactions have been reported (frequency not known):
Nervous system disorders: dizziness, dysgeusia
Ear and labyrinth disorders: Vertigo
Skin and subcutaneous tissue disorders: Alopecia
Musculoskeletal, connective tissue and bone disorders: Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4); joint swelling; stress fractures of the proximal femoral shaft (see section 4.4)
General disorders and administration site conditions: asthenia, peripheral oedema

Laboratory test findings
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 % and 10 %, respectively, of patients taking alendronate 10 mg/day versus approximately 12 % and 3 % of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≥ 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

4.9 Overdose
Alendronate
Hypocalcaemia, hypophosphataemia and upper gastrointestinal adverse reactions, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdose.

No specific information is available on the treatment of overdose with alendronate. In case of overdose with FOSAVANCE, milk or antacids should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Colecalciferol
Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10,000 IU/day. In a clinical study of healthy adults a 4,000 IU daily dose of vitamin D_3 for up to five months was not associated with hypercalciuria or hypercalcaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Bisphosphonates, combinations, ATC code: M05BB03.

FOSAVANCE is a combination tablet containing the two active substances alendronate sodium trihydrate and colecalciferol (vitamin D_3).

Alendronate
Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Colecalciferol (vitamin D_3)
Vitamin D_3 is produced in the skin by conversion of 7-dehydrocholesterol to vitamin D_3 by ultraviolet light. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Vitamin D_3 is converted to 25-hydroxyvitamin D_3 in the liver, and stored until needed.
Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is tightly regulated. The principal action of 1,25 dihydroxyvitamin D_3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

Vitamin D_3 is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary hyperparathyroidism, hypophosphataemia, proximal muscle weakness and osteomalacia, further increasing the risk of falls and fractures in osteoporotic individuals. Supplemental vitamin D reduces these risks and their consequences.

Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations (SD) below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

FOSAVANCE studies
The effect of the lower dose of FOSAVANCE (alendronate 70 mg/vitamin D_3 2800 IU) on vitamin D status was demonstrated in a 15-week, multinational study that enrolled 682 osteoporotic post-menopausal women (serum 25-hydroxyvitamin D at baseline: mean, 56 nmol/l [22.3 ng/ml]; range, 22.5-225 nmol/l [9-90 ng/ml]). Patients received the lower strength (70 mg/2800 IU) of FOSAVANCE (n=350) or FOSAMAX (alendronate) 70 mg (n=332) once a week; additional vitamin D supplements were prohibited. After 15 weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher (26 %) in the FOSAVANCE (70 mg/2800 IU) group (56 nmol/l [23 ng/ml]) than in the alendronate-only group (46 nmol/l [18.2 ng/ml]). The percentage of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D < 37.5 nmol/l [< 15 ng/ml]) was significantly reduced by 62.5 % with FOSAVANCE (70 mg/2800 IU) vs. alendronate-only (12 % vs. 32 %, respectively), through week 15. The percentage of patients with vitamin D deficiency (serum 25-hydroxyvitamin D < 22.5 nmol/l [< 9 ng/ml]) was significantly reduced by 92 % with FOSAVANCE (70 mg/2800 IU) vs. alendronate-only (1 % vs 13 %, respectively). In this study, mean 25-vitamin D, 22.5 to 37.5 nmol/l [9 to < 15 ng/ml]) increased from 30 nmol/l (12.1 ng/ml) to 40 nmol/l (15.9 ng/ml) at week 15 in the FOSAVANCE (70 mg/2800 IU) group (n=75) and decreased from 30 nmol/l (12.0 ng/ml) at baseline to 26 nmol/l (10.4 ng/ml) at week 15 in the alendronate-only group (n=70). There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups.

The effect of the lower dose of FOSAVANCE (alendronate 70 mg/vitamin D_3 2800 IU) plus an additional 2800 IU Vitamin D_3 for a total of 5600 IU (the amount of vitamin D_3 in the higher dose of FOSAVANCE) once weekly was demonstrated in a 24-week, extension study that enrolled 619 osteoporotic post-menopausal women. Patients in the Vitamin D_3 2800 group received FOSAVANCE (70 mg/2800 IU) (n=299) and patients in the Vitamin D_3 5600 group received FOSAVANCE (70 mg/2800 IU) plus an additional 2800 IU vitamin D_3 (n=309) once a week; additional vitamin D supplements were allowed. After 24-weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher in the Vitamin D_3 5600 group (69 nmol/l [27.6 ng/ml]) than in the Vitamin D_3 2800 group (64 nmol/l [25.5 ng/ml]). The percentage of patients with vitamin D insufficiency was 5.4 % in the Vitamin D_3 2800 group vs. 3.2 % in the Vitamin D_3 5600 group through the 24-week extension. The percentage of patients with vitamin D deficiency was 0.3 % in the Vitamin D_3 2800 group vs. zero in the Vitamin D_3 5600 group. There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups. The percentage of patients with hypercalciuria at the end of the 24-week extension was not statistically different between treatment groups.

Alendronate studies
The therapeutic equivalence of alendronate once weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1 % (95 % CI: 4.8, 5.4 %) in the 70 mg once-weekly group and 5.4 % (95 % CI: 5.0, 5.8 %) in the 10 mg daily group. The mean BMD increases were 2.3 % and 2.9 % at the femoral neck and 2.9 % and 3.1 % at the total hip in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

The effects of alendronate on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

In the initial efficacy studies, the mean BMD increases with alendronate 10 mg/day relative to placebo at three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48 % reduction (alendronate 3.2 % vs placebo 6.2 %) in the proportion of patients treated with alendronate experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.

FIT consisted of two placebo-controlled studies using alendronate daily (5 mg daily for two years and 10 mg daily for either one or two additional years):

FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of ³ 1 new vertebral fracture by 47 % (alendronate 7.9 % vs. placebo 15.0 %). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1 % vs. 2.2 %, a reduction of 51 %).

FIT 2: A four year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37 % of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronate 1.0 % vs. placebo 2.2 %, a reduction of 56 %) and in the incidence of ³ 1 vertebral fracture (2.9 % vs. 5.8 %, a reduction of 50 %).

5.2. Pharmacokinetic properties
Alendronate

Absorption
Relative to an intravenous reference dose, the oral mean bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46 % and 0.39 % when alendronate was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.

The alendronate component in the FOSAVANCE (70 mg/5600 IU) combination tablet is bioequivalent to the alendronate 70 mg tablet.

Bioavailability was negligible whether alendronate was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60 %.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

Distribution
Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of alendronate in plasma following therapeutic oral doses are too low for analytical detection (< 5 ng/ml). Protein binding in human plasma is approximately 78 %.

Biotransformation
There is no evidence that alendronate is metabolised in animals or humans.

Elimination
Following a single intravenous dose of [^{14}C]alendronate, approximately 50 % of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95 % within six hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

Colecalciferol
Absorption
In healthy adult subjects (males and females), following administration of FOSAVANCE 70 mg/5600 IU after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}80\ hrs}$) for vitamin D_3 (unadjusted for endogenous vitamin D_3 levels) was 490.2 ng·hr/ml. The mean maximal serum concentration (C_{max}) of vitamin D_3 was 12.2 ng/ml and the median time to maximal serum concentration (T_{max}) was 10.6 hours. The bioavailability of the 5600 IU vitamin D_3 in FOSAVANCE is similar to 5600 IU vitamin D_3 administered alone.

Distribution
Following absorption, vitamin D_3 enters the blood as part of chylomicrons. Vitamin D_3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D_3 at these sites for later release into the circulation. Circulating vitamin D_3 is bound to vitamin D-binding protein.

Biotransformation
Vitamin D_3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D_3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

Elimination
When radioactive vitamin D_3 was administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4 %, and the mean faecal excretion of radioactivity after 4 days was 4.9 %. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of vitamin D_3 in the serum following an oral dose of FOSAVANCE (70 mg/2800 IU) is approximately 24 hours.

Characteristics in patients
Preclinical studies show that alendronate that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see section 4.2).

5.3 Preclinical safety data
Non-clinical studies with the combination of alendronate and colecalciferol have not been conducted.

Alendronate
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition which was related to hypocalcaemia. In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

Colecalciferol
At doses far higher than the human therapeutic range, reproductive toxicity has been observed in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose (E460)
Lactose anhydrous
Medium chain triglycerides
Gelatin
Croscarmellose sodium
Sucrose
Colloidal silicon dioxide
Magnesium stearate (E572)
Butyl hydroxytoluene (E321)
Modified starch (maize)
Sodium aluminium silicate (E554)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

6.4 Special precautions for storage
Store in the original blister in order to protect from moisture and light.

6.5 Nature and contents of container
Wallet with sealed aluminium/aluminium blisters, in cartons containing 2 (1 wallet x 2 tablets), 4 (1 wallet x 4 tablets), 12 (3 wallets x 4 tablets) or 40 (10 wallets x 4 tablets) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER(S)
Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)
EU/1/05/310/006 – 2 tablets
EU/1/05/310/007 – 4 tablets
EU/1/05/310/008 – 12 tablets
EU/1/05/310/009 – 40 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
24 August 2005

10. DATE OF REVISION OF THE TEXT
06 November 2009

completing two volumes of a total of 256 pages.[3] The subsequent three decades saw a dearth in medical journalism and the interim saw the publication of items of medical import in the local newspapers such as *The Malta Times* and *Il Mediterraneo - Gazzetta di Malta*.

The initiative to establish medical journalism was taken up again by Dr. Gavino Gulia who on the 25th July 1871 undertook to publish the medical journal *Il Barth - Gazzetta di Medicina e Scienze Naturali*. Published every forty days, this journal was available by subscription against payment [annual subscription: 8s4d]. This new medical journal achieved a wide subscription so that within two years 90% of doctors practicing in Malta are reported to have subscribed to the journal. Unlike its predecessors, the journal published contributions in both the Italian and English language inviting articles from both Maltese and British practitioners. It discusses various aspects of medical practice on the islands addressing public health concerns, specific medical disorders and innovative management options. It also carried contributions related to botany and natural history reflecting the editor's interests. It continued with regular publication until October 1877. During its six years of publication, *Il Barth* had in its pages striven to bring to the fore the major public health problems influencing the Maltese community besides serving as a medium to furnish continuing medical education for its professional readers.[4]

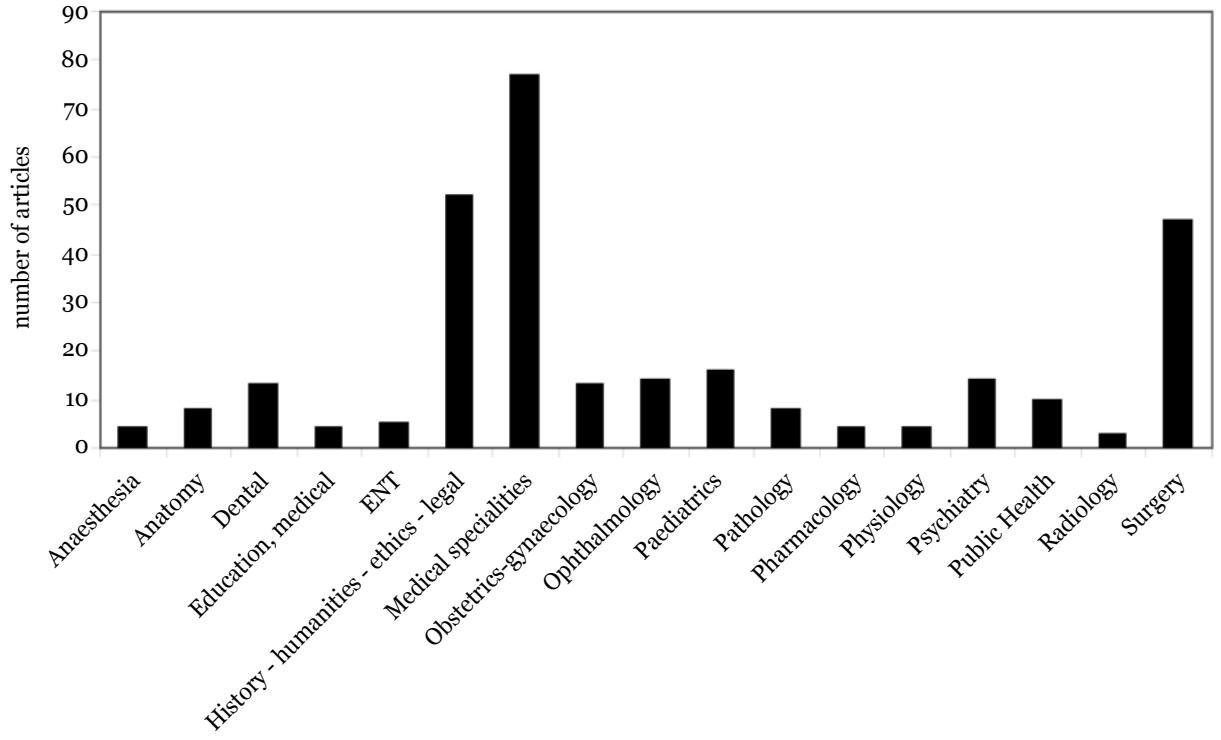
After 1877, medical journalism in Malta again went into hibernation for another thirteen years until the 15th March 1890 when two doctors - Drs. Themistocles Zammit and Fabrizio Borg - undertook the publication of a new fortnightly journal in Italian entitled *La Rivista Medica*. Obtainable by subscription against payment [annual subscription: 6s0d], this journal was to continue publication until the 31st January 1892 having changed editorship to Drs. G. Busuttil and S. Cassar. During its near two-year publication, the journal had described a number of case studies and had outlined several local medical and surgical developments, which included the use of faradic and electrical stimulation in the management of perimetritis and facial palsy, and the performance of elective abdominal surgery and emergency Caesarean section.[5] An attempt was subsequently made to revive *La Rivista Medica* by the *Camera Medica* in July 1922 under the direction of Drs. A. Mizzi and P.P. Debono. This endeavour however was to result only in the publication of four issues, the last journal being published in June 1923.[6]

During the early decades of the twentieth century, the commercial pharmaceutical business owner Mr. Ciro Cherubino set out to edit and publish a medical journal *Il Progresso Medico Chirurgico*. Published during the period December 1920 to October 1921, this journal included contributions dealing with local medical issues and also dealing with advances in therapeutics. It also carried advertisements for patent medicines reflecting the editor's business interests.[7] A similar later publication published by the pharmaceutical import company - A.M. Mangion Ltd. - was the quarterly newsletter *Newsline*, edited by Vincent Briffa, which made its appearance in September 1992 continuing publication until 1995. The scope of this journal was to primarily serve as a newsletter to the company and promote its products. It also carried occasional general articles related to specific pharmaceuticals and items of medical history.[8] A similar commercial-biased journal that primarily serves as a newsletter and service promotion is the publication the *St. Philip's Hospital Newsletter* first published in August 1996 [six issues: 1996-1997] and the currently running *Dear doctor! – The Healthcare newsletter from Saint James Hospital* first published in February 1999.[9,10]

In the latter part of the twentieth century, a move was made to sponsor medical journals through advertisements from commercial businesses, rather then rely solely on reader support. The first initiative of this type was taken by the Malta Branch of the British Medical Students Association [after 1956, the Malta Medical Students Association] who in 1948 published the medical student journal *Chestpiece* with Charles Xuereb as its first editor. The journal served to publish contributions from both medical students and qualified practitioners on various aspects of medical practice, generally of a review nature. The first volume 1948-56 saw the publication of 11 issues, often carrying articles written by university or hospital staff. A supplement to the first volume carried an address by the Minister of Health Dr. A. Schembri Adami who introduced the concept of the National Health Insurance scheme; while in 1949 the journal carried a reprint of Pope Pius XII's pronouncement on artificial insemination and in 1950 carried an article on BCG inoculation by Dr. Andreas Widemann. The publication of the second volume was marked by a significant five year lapse in publication during 1959-63. The contribution in this volume similarly had a strong bias for medical staff contributions. The third volume starting in 1971, in a new format, had a lapse in publication during 1973-74 and 1977-78. The last issue of *Chestpiece* was published in 1979. The first issue of the third volume comments that the editors [J.V. Psaila and D. Vella Briffa] wished "further promoting contributions from students. This issue has had to rely, to some extent, on articles from our competent teachers, but we still feel that the bulk of the contents should come from the student." This policy seems to have been maintained in the subsequent five issues, with the last issue carrying four articles authored by medical students and only one by a member of the medical faculty.[11] The MMSA again embarked with a revived journal named *Mediscope* published during the period 1983-1991 with a total of fourteen issues. The first editor was Mark Bugeja who continued in this role after his graduation.[12] This journal was replaced in 1992 by the medical student journal *Murmur* which serves primarily as a medical student newsletter. The latter journal is still extant.[13]

The publication of a more scientific-based medical publication was undertaken in 1966 by the consultant staff at St. Luke's Hospital, together with the Faculties of Medicine & Surgery and Dentistry. Entitled the *St. Luke's Hospital Gazette*, this biannual journal set out to publish scientific articles reflecting the research activities and interests of the Maltese medical profession. It also received contributions from foreign specialists, including an article on heart transplantation by Prof.

Figure 1: *Subject matter in "St. Luke's Hospital Gazette"*



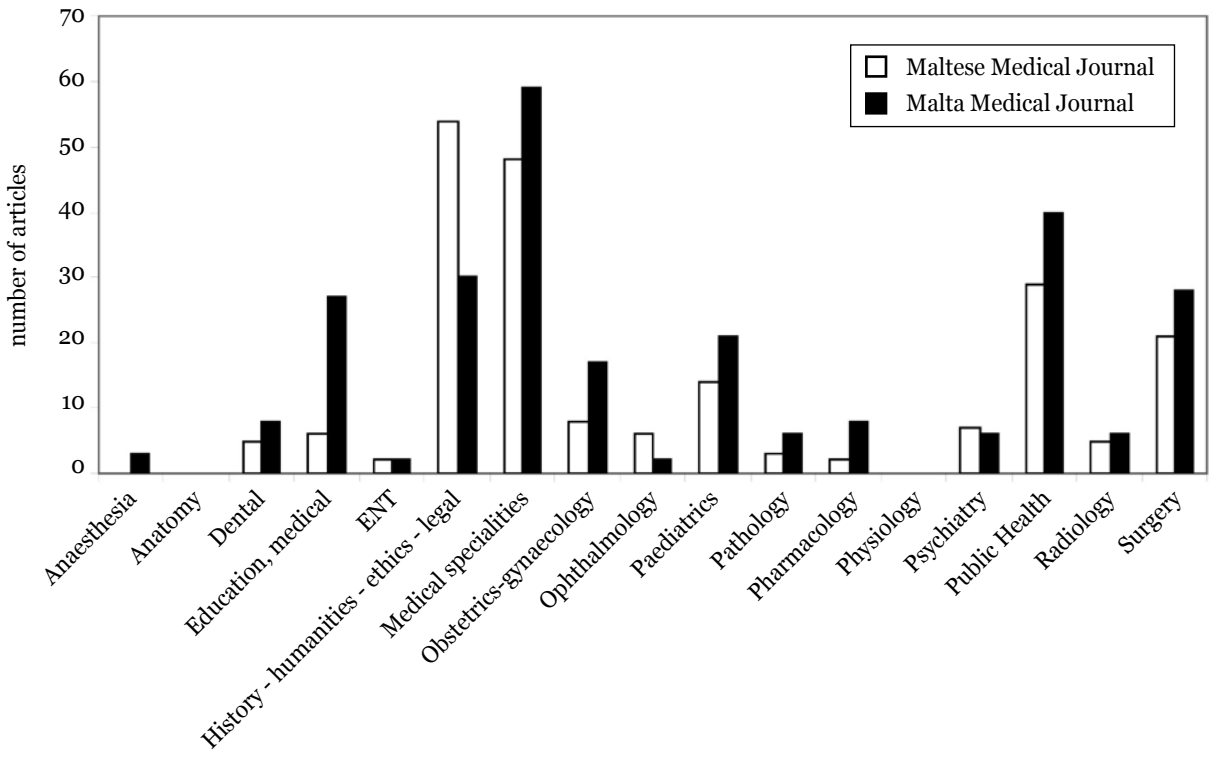
Christian Barnard. There was also a strong bias in contributions related to the humanities as these pertain to medicine. Articles related to the medical humanities, including history, literature, ethics and law, accounted for 17.6% of the contributions. The first appointed editor was Dr. Emmanuel Agius. He was replaced by Dr. Roger Ellul-Micallef in 1975. The publication of this journal was interrupted as a result of the Trade Unionist conflict of 1977. The 11 published volumes had included a total of 296 articles (Figure 1). The last volume published in 1976 is included in the *Pubmed* database.[14]

An attempt was made by the Faculty to re-establish publication of a medical journal in 1982 entitled *Journal of the Malta Medical School*, but these efforts were not successful.[15] A specialist annual journal was published in this interim period by the Association of Anaesthesiologists in Malta - *Acta Anaesthesiological Melitensis* with the aim of serving as a forum for the publication of research and review articles. The first Editorial Board was made up of Drs. N. Boskovski, N. Azzopardi, D. Spiteri, AKMA Zaman and J. Sedlecek. The first issue was published in November 1983. The journal unfortunately ceased publication after six issues in 1989. Besides the anaesthetists and other medical practitioners working in Malta, the journal attracted contributions from other countries such as Denmark, Belgium, Egypt, Czechoslovakia, and Poland.[16] Another professional medical publication issued by a medical association representing a medical speciality is the journal *It-Tabib tal-Familja – Journal of the Malta College of Family Doctors* first published by the Malta College of Family Doctors in 1991. This journal carries a broad selection of contributions generally of a review nature. The journal is still extant and is distributed to all Malta-registered medical practitioners.[17]

The Faculty of Medicine and Surgery did eventually re-initiate the publication of a refereed medical journal in 1989 under the title of *Maltese Medical Journal*, circulated to all the Malta-registered medical and dental practitioners The first series initiated publication under the editorship of Dr. Joseph L. Pace and was published biannually, except in the last two volumes that were published annually. The first series saw the publication of 12 annual volumes with 23 issues. The articles ranged from research articles, review articles, historical articles, and case presentations (Figure 2). It also carried local news items occurring in the medical community.[18]

The journal lapsed publication in 2001, but the Faculty soon re-established a new editorial board under the chairmanship of Prof. J. Cacciottolo and Prof. J. Vassallo as editor. The new board revised the editorial policies and format of the journal now under the title *Malta Medical Journal*. The first issue of the new series was published in November 2002. The frequency of publication was gradually increased to quarterly issues, with supplements that carry the abstracts of the Malta Medical School Conference in 2003, 2006 and 2009. The journal continues to publish articles ranging from research articles, review articles, historical articles, and case presentations (Figure 2). All submitted contributions are peer-reviewed.[19] This journal established itself on the Internet in 2003. This has helped the journal to significantly widen its circulation, so that during 2008

Figure 2: *Subject matter in Maltese Medical Journal* (1989 - 2001) & *Malta Medical Journal (2002 - 20xx)*



the web-version was accessed by a total of 72781 visitors with 230471 page hits annually. Of the visitors, 32298 visited the site only once while 5376 visited more than once. Visitors were the most active from the United States of America and Canada (59804 visitors), the European Union (8708 visitors including 3866 from Malta), other European countries (654 visitors), Australasia (2096 visitors), African continent (263 visitors), with the remainder 1256 visitors were from various countries in the Middle East and South American continent. This increased circulation has helped the journal to achieve recognition and be included in a number of web-based professional databases including Scopus, Index Academicus, and the Directory of Open Access Journals.

Another extant publication is *The Synapse – The Medical Professionals' Network* first launched by Dr. Wilfred Galea in January 2001. This paper-based magazine supplements the web-based service offered by the Medical Professionals' Network on the Internet launched in 1996. The paper-based publication carries short review medical and non-medical articles in an attempt to stimulate continuing professional development. It is distributed free of charge to all Malta-registered doctors, dentists and pharmacists.[20]

The Maltese professional have always strived to promote continuing professional education with efforts to keep updated through reference to foreign journals. The establishment of a regularly published journal further supported the CPE efforts while encouraging the local professionals to adopt a scientific outlook to their practice. These endeavours by the medical profession have been emulated by other paramedical professionals including the pharmacists and midwives who have also published dedicated professional journals.

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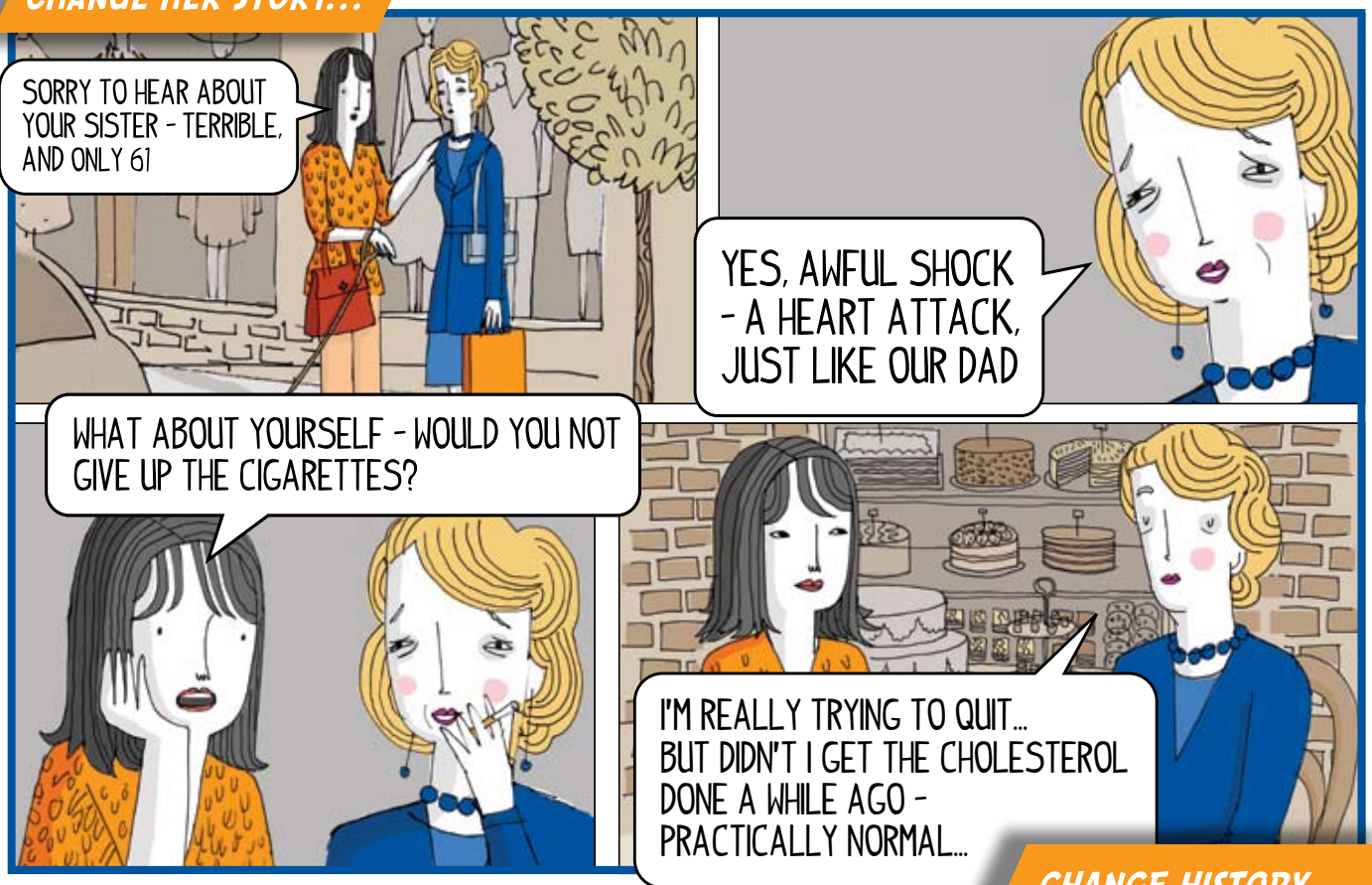

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† NOTE: JUPITER used CRESTOR 20mg. The recommended start dose for hypercholesterolaemia is 5 or 10mg (refer to SPC)

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Abbreviated Prescribing Information CRESTOR® Refer to the full Summary of Product Characteristics (SPC) before prescribing **Presentation:** Film-coated tablets containing 5mg, 10mg, 20mg, or 40mg of rosuvastatin. **Indications:** In patients unresponsive to diet and other non-pharmacological measures, CRESTOR is indicated for primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), homozygous familial hypercholesterolaemia, or mixed dyslipidaemia. Prevention of cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event as an adjunct to correction of other risk factors. **Dosage:** *Treatment of hypercholesterolaemia:* Recommended start dose is 5 or 10 mg daily (including those being switched from other statins). Choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk and potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4 weeks, if necessary. Maximum daily dose is 40mg. A final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when the 40 mg dose is initiated – refer to SPC. Doses may be given at any time of the day with or without food. *Elderly:* A start dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age. *Dosage in patients with renal insufficiency:* Recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of CRESTOR in patients with severe renal impairment is contraindicated for all doses. *Children and adolescents 10-17 years of age:* Paediatric use should only be carried out by specialists – refer to SPC. In heterozygous familial hypercholesterolaemia, the usual start dose is 5mg daily, usual dose range is 5-20mg daily. The 40mg dose is not suitable for paediatric patients. *Children under 10 years:* Safety and efficacy not established. *Race:* Increased systemic exposure in Asian subjects. Recommended starting dose 5mg. CRESTOR 40mg is contraindicated in such patients. *Dosage in patients with pre-disposing factors to myopathy:* The recommended start dose is 5 mg in these patients. The 40 mg dose is contraindicated in some of these patients (see Contraindications). Prevention of cardiovascular events: the dose used in the cardiovascular events risk reduction study was 20mg. **Contra-indications:** Hypersensitivity to any of the ingredients; active liver disease or unexplained persistent elevations in serum transaminases and any serum transaminase > 3 x upper limit of normal; severe renal impairment; myopathy; concomitant ciclosporin; pregnancy and breast-feeding; women of child-bearing potential not using contraception. In addition CRESTOR 40mg is contraindicated with concomitant fibrates, and in patients with predisposing factors for myopathy/rhabdomyolysis including patients of Asian origin (refer to SPC for more information). **Warnings and precautions:** *Renal effects:* Proteinuria which in most cases is transient or intermittent has been observed. Assessment of renal function should be considered during routine follow-up of patients treated with CRESTOR 40 mg. *Muscle effects:* Patients with signs and symptoms of myopathy should be asked to report their symptoms immediately and should have their creatine kinase (CK) levels monitored. CRESTOR should be discontinued if CK levels are markedly elevated or, if muscle symptoms are severe and cause daily discomfort. Risk of myositis and myopathy may increase when administered with certain other drugs (refer to SPC), combination of CRESTOR with gemfibrozil is not recommended for this reason and the benefit versus risk considered when combining CRESTOR with fibrates and niacin. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe and HMG-CoA reductase inhibitors. CRESTOR, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy or rhabdomyolysis (see SPC), and if CK levels are significantly elevated at baseline, treatment should not be started. CRESTOR should not be used in patients with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis. Rarely, rhabdomyolysis, occasionally associated with impairment of renal function has been reported with all doses and in particular doses >20mg. *Liver effects:* CRESTOR should be used with caution in patients with a history of liver disease and/or alcoholism. Liver function tests should be carried out, prior to, and 3 months following the initiation of treatment. CRESTOR should be discontinued or the dose reduced if the level of serum transaminases is greater than 3-times the upper limit of normal. The reporting rate of serious hepatic events is higher at the 40mg dose. *Interstitial lung disease:* Exceptional cases have been reported with some statins, if it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued. *Diabetes Mellitus:* In Patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with Crestor has been associated with an increased risk of diabetes mellitus. The concomitant use of rosuvastatin in HIV patients receiving protease inhibitors is not recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine. **Pregnancy and lactation:** See contra-indications. **Drug interactions:** Also refer to contraindications. CRESTOR is neither an inhibitor nor inducer of cytochrome P450 isoenzymes. CRESTOR may potentiate the anticoagulant effect of Vitamin K antagonists (e.g. warfarin). Decrease in CRESTOR levels seen when co-administered with erythromycin or antacids containing aluminium and magnesium hydroxide. Increase in oral contraceptive level and hormone replacement therapy level is seen when co-administered with CRESTOR. Concomitant use of CRESTOR and gemifibrozil resulted in a 2-fold increase in rosuvastatin Cmax. Concomitant use of CRESTOR and ezetimibe resulted in no change in AUC or Cmax for either drug; however a pharmacodynamic interaction in terms of adverse events cannot be ruled out. Protease inhibitors. **Undesirable effects:** Common: headache, dizziness, constipation, nausea, abdominal pain, myalgia, asthenia and diabetes in patients with fasting glucose 5.6 to 6.9mmol/L. Uncommon: pruritus, rash and urticaria. Rare: myopathy (including myositis), rhabdomyolysis, hypersensitivity reactions including angioedema, increased hepatic transaminases, pancreatitis. Very rare: jaundice, hepatitis, haematuria, polyneuropathy and memory loss and arthralgia. Other usually transient side effects: elevation in CK levels, proteinuria. Other adverse events listed as unknown: diarrhoea, Stevens-Johnson syndrome, oedema, cough and dyspnoea. The following adverse events have been reported with some statins: depression, sleep disturbances including insomnia and nightmares, sexual dysfunction and exceptional cases of interstitial lung disease, especially with long term therapy. **Legal Category:** POM. **Marketing Authorisation Number (s):** PA 970/57/1-4. **Marketing Authorisation Holder:** AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, UK. Further information is available on request from: AstraZeneca Pharmaceuticals (Ireland) Ltd., College Park House, 20 Nassau Street, Dublin 2 Telephone: (01) 6097100; Updated 06/10 CRESTOR is a trademark of the AstraZeneca group of companies. Licensed from Shionogi & Co Ltd, Osaka, Japan. **Date of preparation:** July 2010. **URN:** 10/0396.

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Onbrez Breezhaler (indacaterol) inhalation powder, hard capsules
PRESENTATION: Onbrez Breezhaler 150mcg and 300mcg inhalation powder hard capsules containing indacaterol maleate, and separate Onbrez Breezhaler inhaler. **INDICATIONS:** For maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** Recommended dose is the inhalation of the content of one 150mcg capsule once a day, administered at the same time of the day each day, using the Onbrez Breezhaler inhaler. Capsules must not be swallowed. Dose should only be increased on medical advice. The inhalation of the content of one 300mcg capsule once a day has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. Maximum dose is 300mcg once daily. No dose adjustment required in elderly patients, for patients with mild and moderate hepatic impairment or for patients with renal impairment. No data available for use in patients with severe hepatic impairment. No relevant use in the paediatric population. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, to lactose or to any of the other excipients. **WARNINGS/PRECAUTIONS:** ***Asthma:*** ♦ONBREZ BREEZHALER SHOULD NOT BE USED IN ASTHMA. ***Paradoxical bronchospasm:*** ♦ If paradoxical bronchospasm occurs Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted. ***Deterioration of disease:*** ♦ Not indicated for treatment of acute episodes of bronchospasm, i.e. as rescue therapy. ***Systemic effects:*** ♦Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. ***Cardiovascular effects:*** ♦ Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes. In case such effects occur, treatment may need to be discontinued. ***Hypokalaemia:*** ♦ Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. ***Hyperglycaemia:*** ♦Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients. ♦During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1-2% on Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus. ***Pregnancy and Lactation:*** ♦No data available from the use of indacaterol in pregnant women. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. ♦Not known whether indacaterol / metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or discontinue Onbrez Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **INTERACTIONS:** ♦Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists. ♦Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. ♦Indacaterol should not be given together with beta-adrenergic blockers (including eye drops) as these may weaken or antagonise the effect of beta2-adrenergic agonists. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. ♦Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler. ♦Indacaterol has not been shown to cause interactions with co-medications. **ADVERSE REACTIONS:** ♦The most common adverse reactions with Onbrez Breezhaler are: nasopharyngitis, upper respiratory tract infection, sinusitis, diabetes mellitus and hyperglycaemia, headache, ischaemic heart disease, cough, pharyngolaryngeal pain, rhinorrhoea, respiratory tract congestion, muscle spasm, peripheral oedema. ♦Uncommon: paraesthesia, atrial fibrillation and non-cardiac chest pain. ♦Please refer to SmPC for a full list of adverse events for Onbrez Breezhaler. **LEGAL CATEGORY:** **POM PACK SIZES:** Onbrez Breezhaler 150mcg - carton containing 10 or 30 capsules and one Onbrez Breezhaler inhaler. Onbrez Breezhaler 300mcg - carton containing 30 capsules and one Onbrez Breezhaler inhaler **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/593/001, 002, 007 Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office P.O Box 124, Valletta, VLT 1000 Malta. Tel: +356 22983217 2010-MT-01-ONB-16-Jun-2010

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- Evidence-based medicine including the ADVANCE study, the largest morbidity-mortality trial in diabetes[1-5]
- First scored modified release formulation allowing progressive titration[6]
- Efficient glycemic control with well proven tolerability and weight neutrality[1,2,7]
- Protective on the β-cell[8,9] and the cardiovascular system[1,3,5,10]

1. The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572. **2.** The GUIDE Study. *Eur J Clin Invest.* 2004;34:535-542. **3.** The STENO 2 Group Study. *N Engl J Med.* 2008;358:580-591. **4.** The CONTROL Study. *Diabetologia.* 2009;52:2288-2298. **5.** Khalangot M, Tronko M, Kravchenko V et al. *Diabetes Res Clin Pract.* 2009;20(6):611-615. **6.** Diamicron MR 60 mg. *Product Monograph.* **7.** Drouin P. and the Diamicron MR Study Group. *J Diabetes Complications.* 2000;14:185-191. **8.** Sawada F, Inoguchi T, Tsubouchi H, et al. *Metabolism.* 2008;57(8):1038–1045. **9.** Del Guerra S, D'Aleo V, Lupi R, et al. *Diabetes Metab.* 2009;35(4):293-298. **10.** Katakami N, Yamasaki Y, Hayaishi-Okano R, et al. *Diabetologia.* 2004;47:1906-1913.

Composition: Each modified-release tablet contains 60 mg of gliclazide. **Indication:** Type 2 diabetes. **Dosage:** One half to 2 tablets per day, ie, 30 to 120 mg as a single daily intake at breakfast time, including in elderly patients and those with mild to moderate renal failure. One DIAMICRON 60 mg modified release tablet is equivalent to two DIAMICRON 30 mg modified release tablets. The breakability of the DIAMICRON 60 mg modified release tablet enables flexibility of dosing to be achieved. **Properties:** Diamicron MR 60 mg is a sulfonylurea lowering blood glucose levels by stimulating insulin secretion thereby restoring the first peak of insulin secretion and increasing the second phase of insulin secretion in response to a meal or intake of glucose. Independent hemovascular properties. No active circulating metabolite. **Contraindications:** Hypersensitivity to sulfonylureas or sulfonamides, type 1 diabetes, diabetic precoma and coma, diabetic ketoacidosis, severe renal or hepatic insufficiency, treatment with miconazole, breast-feeding. **Interactions:** Increased risk of hypoglycemia with miconazole, phenylbutazone, alcohol, other antidiabetics, β-blockers, fluconazole, ACE inhibitors, H_2-receptor antagonists, MAOIs, sulfonamides, NSAIDs. Risk of hyperglycemia with danazol, chlorpromazine, glucocorticoids, β_2 agonists, ritodrine, salbutamol, terbutaline, anticoagulants. **Adverse effects:** Hypoglycemia, gastrointestinal disturbance; more rarely: skin and subcutaneous reactions, hematological disorders, hepato-biliary disorders, visual disorders. **Overdosage:** Possible severe hypoglycemia requiring urgent IV glucose and monitoring. Please refer to the complete summary of product characteristics for your country as variations may exist. LES LABORATOIRES SERVIER France, Correspondent: SERVIER INTERNATIONAL: 35, rue de Verdun, 92284 Suresnes Cedex, France. **www.servier.com**

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1 to 2 tablets* at breakfast

*In most patients

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chief interventionist being Disraeli.

Possibilities were very good. With Constantinople in British and French hands, the Russian army could be supplied. The Czar government secure from its internal enemies - the Bolshevists – could initiate a new Russian offensive in the East, thus relieving the Western Front from pressure.

Churchill thought that the Dardanelles could be forced by the navy alone. In conjunction with the French, the British sent the pre-dreadnaughts. This led to a major disaster, the Turkish waters were infested with mines and the approaches with heavy fortified forts. The allies lost a number of battleships through enemy activity and German submarines were reputed to be in the area. Hence it was thought that the Gallipoli Peninsula should be cleared of the hostile troops by landing troops on it – the Anzacs, Austrialian and New Zeland troops who were in Egypt at that time. However, the element of surprise had been lost and when the troops finally landed they found the Turkish troops ready for them. No real progress was done and after a few months, in which thousands of Allied troops were either killed or wounded, they were evacuated from the Gallipoli beaches, Winston Churchill resigned and eventually the Czar regime collapsed. Luckily the United States came into war on the side of the allies and the Western front was saved.

Malta was warned to get itself prepared to receive the wounded of the Gallipoli campaign. The Governor at that time was Lord Melhuen who was a very good organiser. Plans were immediately started to turn Malta into a giant hospital. At that time there were four hospitals in Malta, the Central Hospital for civilians, the Blue Sisters' hospital for merchant seamen, Bighi hospital for the navy and Mtarfa Hospital for the army. Their total capacity was about three hundred beds, if all the rooms and available space were utilized there would be five hundred beds – far short of what was necessary. The Holy Infirmary at Valletta was roped into service. Some new schools were turned into hospitals and barracks which had been vacated by the troops turned into hospitals. Originally Allied command in Egypt asked for 3000 beds. However, with mounting injuries it was soon found that that extimate was not nearly enough and more bed space was created. A hospital is totally useless without adequate staff, doctors, nurses, attendants, labourers, technicians, cooks, laundry people, etc., etc.

The soldiers invaded the Gallipoli Peninsula on the 25th April 1915. Many soldiers were wounded or killed. Up to the end of May 1915, 38,000 soldiers were either killed or wounded. These figures will make us understand the extent of the problem facing the authorities over here. The first wounded reached Malta on the 4th May 1915. They were carried on hospital ships, painted white with a big red cross painted on their sides. When the people realized that the wounded of Gallipoli were entering the bastions, the mood was very sombre. The harbour had the aspect of a sick ward in a general hospital, silence all around.

One thousand two hundred solders, wounded from the front were brought on that day. Barges went against the hospital ships and the injured soldiers were brought down very gently by the cranes on stretchers and from the barges onto the shore. From the quay they were taken to the Holy Infirmary at Valletta where they were examined by top British and Maltese doctors, from there they were sent to other centres according to their injuries. A Maltese doctor appointed by the Governor himself for such duties was Dr Robert Randon who was placed in charge of Fort Tigne, now turned into a hospital of about 1,000 beds.

The processes of wounded soldiers on stretchers drawn by mules and horses passed through Kingsway, now Republic street, in Valletta on its way to the Holy Infirmary. It was described as that of Good Friday, silence reigned and people on each side on the pavements welcomed the soldiers with cigarettes, sweets, flowers and chocolate. The wounded soldiers most of them very young showed their appreciation by waving to the people and from that day the close bond between Malta and Australia was born. Indeed a lot of these soldiers died in Malta and they were buried at Braxia Cemetery at Pietà near where the football club now stands.

May I be permitted here to read Rupert Brooke poem The Soldier written in that period of time.

If I should die, think only this of me
That there in a corner of a foreign field
That is forever England. There shall be
In that rich earth a richer dust concealed.
A dust whom England bore, shaped, made aware
Gave, once, her flowers to love, her ways to name,
A body of England's , breathing English air,
Washed by the XX, blast by suns of home.

Perhaps if we were to substitute Australia for England here, we can better understand the atmosphere, the sorrow and anguish that reigned in Malta that summer of 1915.

Up till the end of May, 4000 wounded had arrived and they were bring treated in 8 hospitals. By September, 10,000 wounded had arrived. By March 1916, there were 20,000 hospital beds, in all 80,000 soldiers were treated in Malta. A percentage of them found their grave in Malta. Military funerals were the order of the day, sometimes with eight or more dead soldiers buried on the same day. Since these funerals were having a depressing effect on the general population, it was decided to conduct them from outside the limits of Floriana, from Portes des Bombes to Braxia cemetery.

The Gardens of Argotti, the Mall, and the streets of Valletta were all full of wounded soldiers. Some of them had an amputated arm pushing at colleague in a wheelchair with amputated legs. Some had bandaged heads, others were blind. However, they were cheerful and made friends with the Maltese people who opened the doors of their homes and hearts to them. Ladies organised tea parties and concerts for them. They started to sponsor children by giving them cards found in cigarette boxes. In general the soldiers who survived the Gallipoli experience were quite happy for things could have been far worse for them. In all they were treated in 27 military hospitals, one of them being the newly built school of Sliema. Archbishop Caruana was asked to tell the parish priests not to

ring the bells to let the patients rest. The Archbishop obliged and the bells stopped ringing.

Ghajn Tuffieha was tunred into a giant camp for convalescent soldiers. In all there were 4,000 beds under tents. Three hundred civilian and military doctors were employed. Some top British surgeons came to Malta, like Balance and Garrod, and 1000 British nurses came from the UK.

Gradually things started to calm down. It was obvious that the Allies were making no headway in Gallipoli and they were pushed back. However, on the 25th December 1915 the British and the French landed in Salonika to help the Serbians. The First World War started from Serbia. In the Balkan wars of 1911 and 1912, Bulgaria was offered Macedonia but its share went to Greece and Serbia. Hence Serbia was attacked by Bulgaria, and the British and French went to help. This time the Maltese makeshift hospitals were filled with malaria and typhoid. It is interesting to note that the first cardiac operation was done in Malta on a soldier who had been shot by a Bulgarian sniper.

As the Gallipoli and Salonika campaigns subsided so did the Maltese hospitals empty, to fill again by the Spanish Influenza victims. Employment during the war and when the war finished there was massive unemployment in Malta. A lot of ships had been sunk, food was scarce and hard to get, there was massive inflation and the safety valve of emigration non-existent since Australia had problems of its own. With political aspirations on the increase, the unemployed workers looked at the political leaders like Sir Filippo Sciberras and the next scene was the Sette Gungio rites of 1919.

When the First World War was nearly over the so-called Spanish Flu appeared. The pandemic killed more people than the war itself, although one can attribute it to the war itself. When there is mass movement of troops and civilians with the most basic requisites of hygiene ignored and non-existent, one can expect epidemics. In WW1 Spain was neutral and the first reported cases came from Spain since the censorship of the media was free. It appeared in the US where young people were being called for service in Europe by Widrow Witson, thousands died in their training camps. It infected the allied army in Northern France where a depot was located and then spread to the German army. In all there were three waves of this pandemic and it was characterized by fever, breathing problems, haemoptysis and cyanosis. Hence our hospitals started to fill again on the 4th October 1918. The Government issued regulations to prevent the spread of the disease – avoiding overcrowding and general cleanliness. Between the 1st September 1918 and 1st March 1919 there were 651 deaths. March was the high point of the third wave. The Influenza continued onto 1920. In February and March 656 cases were reported with a mortality of over 30%. The total mortality of the 1918 – 1919 pandemic in Malta was 3 per 1000 of the population.

On the 10th December 1917 His Excellency the Governer declared at the beginning of the session of the Council of Government. "I also desire to record my grateful recognition of the sympathetic hospitality which the people of Malta and Gozo have extend to the sick and wounded that have been brought during the war, of the support that they have given to the British Red Cross and the Order of St John of Jerusalem and the other charitable institutions that have been formed." This was not the first time that Malta took the role of a Nurse in Wartime and it is said that Malta had added a bright chapter to human history and the severance to its hospitals ever be named; for their sacrifice has once more been enthroned, and unselfishness, garbed in nurses' cape or surgoens' uniform, proclaimed the triumph of love.