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10 years in the service of the profession

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Over 10 years ago two pharmacists got together and identified a gap in the professional development opportunities of pharmacists. They felt the need to address this gap and immediately teamed up with other pharmacists to help with the task at hand. A considerable amount of work followed, including a study of provision of continuing education systems in other countries and in other professions.

Pharmacists in Malta were surveyed to be able to identify their willingness to participate in such events and their educational practice needs. They were consulted over a variety of issues including timing of meetings and social issues such as planning meetings during periods when pharmacists who were parents were not in heavy demand at home. Meetings were never scheduled for Mondays as this tends to be a very hectic day for pharmacists practicing in community and neither were they scheduled on a Friday as this signifies the start of the weekend.

Based on feedback from the survey together with consultation with expert pharmacists and national health priorities, a programme was formulated and mailed to all registered pharmacists in Malta. It was decided that the College would run as a pilot for a year to determine its viability, before being officially launched.

The following is an excerpt from the introduction to the first programme:

'The strength of this initiative lies in our youth and enthusiasm for the profession. We feel that Maltese pharmacists have as much potential as their foreign counterparts but lack the proper infrastructure for professional development... These workshops provide the opportunity for all pharmacists to actively participate by pooling their acquired knowledge and experience'.

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The first session was held on the 8th March 1995, at the Department of Pharmacy, University of Malta. It addressed weight loss and food supplements and was delivered by Ms Claire Copperstone, a pharmacist and nutritionist.

The response far exceeded our expectations. We have since based our activities on the same principles that we declared initially i.e. our enthusiasm for the profession, the potential of pharmacists in Malta, active participation and pooling and building upon pharmacists' acquired knowledge and experience.

Having drawn up a statute, The Malta College of Pharmacy Practice was officially launched on the 31st July 1996. From its conception the College has chosen to follow this philosophy of Pharmaceutical Care defined as 'the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life….. Pharmaceutical care is provided for the direct benefit of the patient and the pharmacist is responsible directly to the patient for the quality of that care'.[1]

The Malta College of Pharmacy Practice is an autonomous academic institution that has been established to facilitate the participation of pharmacists in life-long learning, thereby contributing to their professional development. The ultimate aim is to provide pharmacists with the necessary tools to offer the best possible care and service to the patient.

In the summer of 1997 the need to keep in touch with pharmacists over the summer period was felt in addition to the weekly meetings in winter and autumn. Thus the first edition of the Chronic*ill was issued. At the time the format was more of a news letter. By 1999 it was transformed into a scientific peer reviewed journal and later also obtained an ISSN number.

The title of the Journal went through a transition period last year and is now officially called The Journal of the Malta College of Pharmacy Practice. The Journal has a circulation of over 2000 and is distributed to all pharmacists and all medical doctors in Malta. The rationale behind distributing to medical doctors is to enhance professional collaboration and communication. The Journal is also mailed to specific institutions abroad.

The College is today an internationally recognised institution and willingly collaborates with other institutions both locally and internationally in the interest of the professional development of pharmacists in all areas of practice.

In July 2004 the College organised and hosted the 13th International Social Pharmacy workshop entitled "Social Pharmacy: Theoretical and Cultural Perspectives." The meeting, which was held for the first time in the Mediterranean region, welcomed 140 delegates from 30 countries making it one of the largest social pharmacy gatherings held to date. This was truly an accomplishment for the College, and it provided pharmacists practicing in Malta with the opportunity to network with international colleagues as well as to present their work at an international forum.

In July 2005 the College and the Journal featured prominently in an article published in the German pharmacy Journal Deutsch Apoteheker Zeitung describing pharmacy in Malta as part of a series regarding pharmacy in the new EU member states.

Over the years the College has continued to grow and expand remaining mindful of the needs of its members. This year the College registered the highest number of members ever. It has also seen, with significant pride, a growing professional maturity, increasing assertiveness and professional pride amongst its members. Over time, the image of the College has changed and a more attractive logo was introduced.

Quality improvement is an ongoing process conducted by the council which is constituted entirely by voluntary members. Feedback and constructive criticism from members is encouraged and taken into consideration. Action has also been taken regarding issues raised by members related to professional practice. Members of the council sit on various committees representing the interest of the professional practice of pharmacy in Malta.

We would like to encourage members to take a more active role at the management and administrative level of the College in order to enable us to meet the ever increasing educational needs of pharmacists.

I would like to thank all members of the council past and present who have worked selflessly in the interest of the profession and to strengthen the College.

In the name of the Council I would also like to thank all those who have in any way supported the work of the College over these past 10 years and look forward to a challenging future together.

Reference

1. Hepler and Strand. Opportunities and responsibilities in pharmaceutical care. American Journal of Hospital Pharmacy 1990; 47:533-543.

Patient safety

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"If healthcare was an airline, only dedicated risk takers, thrill seekers and those tired of living would fly on it"[1]

Over the past five years, patient safety as a topic of academic interest has blossomed, with numerous books and research articles being published. Yet, the concept of patient safety is not new. Even the rule attributed to Hippocrates has it at its core: the doctor should "first, do no harm". However, it has really only been recently that the frequency and consequences of medical error have really been brought to the public's attention.

A trigger for this was the publication of the report "To Err is Human: Building a Safer Health System" in the United States of America (USA).[2] This document concluded that deaths due to medical error were comparable to that due to breast cancer or road traffic accidents. Patient safety became a discrete topic of scholarly activity rather than part of the wider sphere of health care quality. Recently, for example, the World Health Organisation (WHO) has launched the World Alliance for Patient Safety[3] and, in its European region, has devoted one of its Futures Forums to the governance of patient safety.[4]

Patient safety has been defined as "the avoidance, prevention and amelioration of adverse outcomes or injuries stemming from the process of health care".[1] Although it applies to the delivery of all healthcare, most research activity has concentrated on high risk areas, such as surgery, obstetrics, and medicines. To illustrate some of the main topics of interest, this article concentrates, as an example, on patient safety as it is related to medication use during hospital care.

In this example, patient safety is about more than the prevention of prescribing errors; it is about the reduction of patient harm. Some of that harm is preventable, such as that caused by prescribing errors; some harm is not, such as that caused by unpredictable adverse drug events (ADEs). Nonetheless, there is a lot that can be done to ameliorate the morbidity suffered by patients in such cases. The National Patient Safety Agency in the United Kingdom (UK) has coined the term "patient safety incident", to describe any unintended or unexpected incident which could have or did lead to harm for one or more patients.[5] Patient safety incidents include "near misses", where potential for harm existed that did not actually occur, either due to good fortune or the vigilance of staff. This term concentrates on actual patient outcome, therefore, rather than the process of care that led to that outcome.

The epidemiological work conducted on the frequency of patient safety incidents has produced some alarming statistics. In a groundbreaking study conducted in New York in the 1980s, the authors found that almost 4% of patients admitted to hospital suffered "disabling injuries" due to patient safety incidents, with more than a quarter due to negligence; 14% of those injuries were due to medicines.[6] A recent systematic review concluded that approximately 4.5% of admissions to hospital had drug-related morbidity as a primary cause or contributing factor.[7] During the hospital stay, ADEs occur in up to 6.5% of admissions, prolonging the stay by almost 2 days. This costs an additional $2,000 and increasing the risk of death for the patient by a factor of nearly 2.[8,9] More worrying, it has been estimated that 25-50% of such ADEs are preventable[8,10] and that these preventable ADEs are more severe, with double the hospital stay and costs of other ADEs.[8]

Studies of ADEs, by definition, concentrate on incidents with negative outcomes to treatment. Investigations of medication errors (including prescribing and administration errors) are concerned with incidents that *may* cause harm, but often don't. However, they are very useful in understanding the causes of these types of patient safety incidents. It has been estimated that prescribing errors occur in 0.4 to 1.9% of all prescriptions written in the USA and UK.[11-14]

Patient safety incidents due to errors can occur at any stage during the medication process, from decision-making to administration. However, they seem to occur most frequently when patients move between primary and secondary care, i.e. at the time of admission to or discharge from hospital.[15,16] For example, lack of information about what was prescribed to a patient in the community may result in the failure to continue essential drugs. Poor communication with the general practitioner may result in unnecessary changes to the discharge medication. During the admission, numerous distractions during a busy ward round could result in transcribing errors, with a junior doctor writing bumetanide 5mg, instead of bendroflumethazide 5mg. And in the pharmacy, a simple slip of the hand could result in an inexperienced pharmacist dispensing a box of lorazepam 1mg tablets against a prescription for lorazepam 2.5mg tablets.

These examples can be used to highlight the systems approach to human error proposed by Reason.[17] Contrary to the person approach that is commonplace (where individuals are personally blamed for their forgetfulness etc), in the systems approach efforts are concentrated on understanding the conditions under which people work and how failure of the systems contribute to error occurrence. Thus, amelioration focuses on building defences to prevent errors or reduce their impact. The errors described above have the *potential* to cause ADEs. However, many times when such errors occur, this does not happen. The prescription for bumetanide 5mg could have been identified by a clinical pharmacist who was alarmed at such a high starting dose. The prescription for lorazepam would have been double checked by another and re-dispensed before being given to the patient.

This systems approach considers that most errors are caused not by "bad people", but by defects in a system, whereby the person actually causing the error may be the final link in a long chain. For example, a nurse on a very busy ward might not have a drug calculation checked by her sole colleague (who was with another patient) and therefore administer a twofold overdose of digoxin injection to patient. There were (at least) two systems problems here, leading to the patient safety incident. Firstly, poor training in drug calculations did not prepare the nurse for what she had to do on a busy ward with numerous distractions. Secondly, the ward was short of staff and no one was available to conduct the check at the required time. Rather than not treat the patient, the nurse choose to go against the protocol and administer the drug anyway. The study of such incidents from a systems perspective can help us to understand how to improve the situation (e.g. better training and increased staffing levels) and prevent further incidents, rather than pillory a series of unfortunate "culprits".[17]

There are many potential interventions that have been shown to improve patient safety with medicines. These include information technology,[18] clinical pharmacy services,[19] and better transfer of information between primary and secondary care.[15,16] However, it is also important to think more broadly about improving patient safety. The WHO's Futures Forum on the governance of patient safety described what they called the "seven deadly sins" in dealing with patient safety (Table 1).[4] If clinicians believe or pretend to believe that mistakes do not happen, or try to cover them up for fear of blame, then it is impossible to learn and improve patient safety. The solutions recommended in the WHO report are not interventions directed at the "sharp end" of the problem (i.e. the individual healthcare professional), but at the overall systems within which they provide care.

There needs to be both political and professional will to address patient safety at a national level. Locally, there needs to be strong leadership and a willingness to change the prevailing culture from one of blame for the slightest mishap, to an open and fair culture where people take responsibility for patient safety. There also needs to be good quality data available that can be used to describe the problem and show that change is necessary and possible. Learning from our mistakes is a normal part of the human condition. In the working life of a single healthcare professional, however, one would hope that they would not make enough mistakes to learn all that they need to know! Therefore, we need to learn also from the mistakes of others. The WHO has published draft guidelines on using patient safety incident reporting to improve patient safety.[20] For example, the National Reporting and Learning System for patient safety problems in the UK is a central repository to draw together reports of patient safety incidents and system errors from across the country to help the National Health Service learn from such mistakes.[5]

Improving patient safety is something that all health care professionals aspire to. This short article gives a brief overview of some of the current thinking in the area. Recognition of the problem and an openness to learn from mistakes will take us far. As has been said before, "those who cannot remember the past are condemned to repeat it".[21]

Table 1

The "seven deadly sins" in recognising and addressing patient safety[4]

- Arrogance
- Denial
- Blame
- Shooting the messenger
- Averting the gaze
- Failure to think systems
- Passive learning

References

1 Vincent C. Patient safety. Edinburgh : Elsevier Churchill Livingstone; 2006.

2 Kohn L, Corrigan J, Donaldson M. To err is human: building a safer health system. Washington, DC: National Academy Press; 2000.

3 World Health Organisation. World Alliance for Patient Safety. http://www.who.int/patientsafety/worldalliance/en/ [accessed 15 June 2006]

4 Arnaudova A, Jakubowski E. Eighth Futures Forum on Governance of Patient Safety. Copenhagen, Denmark: WHO Regional Office for Europe; 2005.

5 National Patient Safety Agency website. http://www.npsa.nhs.uk [accessed 15 June 2006]

6 Leape,L.L.; Brennan,T.A.; Laird,N.; Lawthers,A.G.; Localio,A.R.; Barnes,B.A.; Hebert,L.; Newhouse,J. P.; Weiler,P.C.; Hiatt,H. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med 1991 Feb 7;324(6):377-84.

7 Winterstein AG, Sauer BC, Hepler CD, Poole C. Preventable drug-related hospital admissions. Ann Pharmacother 2002 Jul;36(7-8):1238-48.

8 Bates,D.W.; Spell,N.; Cullen,D.J.; Burdick,E.; Laird,N.; Petersen,L.A.; Small,S.D.; Sweitzer,B. J.; Leape,L.L. The costs of adverse drug events in hospitalized patients. JAMA 1997;277:307-11.
9 Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1997;277:301-6.
10 Lindley CM, Tully MP, Parmasothy V, Tallis RC. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. Age Ageing 1992;21:294-300.
11 Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA 1997;277:312-7.
12 Folli HL, Poole RL, Benitz WE. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics 1987;79:718-22.
13 Blum KV, Abel SR, Urbanski CJ. Medication error prevention by pharmacists. Amer J Hosp Pharm 1988;45:1902-3.
14 Dean B, Schachter M, Vincent C, Barber N. Prescribing errors in hospital inpatients: their incidence and clinical significance. Qual Saf Health Care 2002 Dec 1;11(4):340-4.
15 Midlov P, Bergkvist A, Bondesson A, Eriksson T, Hoglund P. Medication errors when transferring elderly patients between primary health care and hospital care. Pharm World Sci 2005;27:116-20.

Practice Points

- Patient safety incidents associated with medicines, such as prescribing errors and adverse drug events, are very common both in hospitals and in family practice in the community.
- Such incidents cause considerable morbidity and mortality to the patients and waste large quantities of health care funding.
- International researchers and policy thinkers agree that taking a systems approach and learning from the mistakes of others are two methods that can be used to improve patient safety
- They also agree that denial of the problem and blaming the individual, who makes a mistake when working in a system riddled with error-producing conditions, are counterproductive efforts.

16 Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care 2006 Apr;15(2):122-6.
17 Reason J. Human error: models and management. BMJ 2000 Mar 18;320(7237):768-70.
18 Bates DW, Gawande AA. Patient Safety: Improving Safety with Information Technology. N Engl J Med 2003;348:2526-34.
19 Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes (Cochrane review). The Cochrane library. Issue 3 ed. Chichester, UK: John Wiley & Sons, Ltd; 2004.
20 World Alliance for Patient Safety. WHO Draft Guidelines for Adverse Event Reporting and Learning Systems. From Information to Action. Geneva, Switzerland: World Health Organisation; 2005.
21 Santayana G. The life of reason; or, The phases of human progress. [2nd ed.] ed. London : Constable & Co.; 1906.

Pharmacotherapeutic approaches in the treatment of Alzheimer's Disease

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Keywords: Alzheimer's disease, pharmacotherapy, acetylcholinesterase inhibitors, galantamine, rivastigmine, donepezil, memantine.

Alzheimer's disease (AD) is the most common form of dementia and accounts for major cognitive impairment in the elderly. It is a progressive neurodegenerative disorder with distinct pathology. At present, the pharmacotherapy of AD involves the use of acetylcholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. The former imply neuroprotection hence slowing disease progression while the latter may block neuronal excitotoxicity.

Introduction

AD is the most common form of dementia accounting for about 50-60% of the cases. Its prevalence increases exponentially, from about 2-3% of the population at age 65 to nearly 47% after the age of 85. Given the trend towards an increase in the elderly population, the prevalence of AD is expected to double in the next forty to fifty years. Although no epidemiological studies have been carried out locally, it is estimated that the number of current cases in Malta almost reaches the 4,000 figure. In addition to the huge costs of treating AD, its psychological and social burden on caregivers and society are enormous. Caregivers usually become depressed, increasing their own use of medical resources, and are forced to reduce or terminate employment. Therefore, any interventions that slow down the rate of disease progression even modestly will have a major impact on public health.[1]

AD is an insidious neurodegenerative malady characterised by the presence of amyloid plaque deposits and neurofibrillary tangles in the brain in association with significant loss of cholinergic cell population in areas of the brain associated with learning and memory formation.[2] These pathological lesions and imbalance in cholinergic neurotransmission accelerate neuronal death.

The first stages of the disease is principally characterised by a decline in memory, especially loss of recent memory. Increasing signs of faulty judgment and personality changes also occur during this stage. At a later stage, memory decline worsens whereas language, attention, and executive functions become gradually impaired with patients losing the ability to perform activities of daily living such as dressing, washing and eating. Finally, the disease becomes so debilitating that the patients become mute, incontinent and unable to walk, with the consequence of becoming bedridden and prone to illness and infection.[3]

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors (AChEIs) were the first pharmacological treatments for AD approved by the US Food and Drug Administration (FDA). Currently four AChEIs are clinically available: tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®). Their major therapeutic effect is reported to be their ability to maintain cognitive function compared with placebo over a three year treatment period or even less.[4,5] Some studies also suggest that these drugs can stabilise and even reverse the neurotoxic effects of AD thus delaying the disease progression, especially if administered early in the course of the disease benefiting patients with mild to moderate AD.

Rivastigmine is also capable of blocking the action of another cholinesterase enzyme, butyrylcholinesterase (BuChE), which increases considerably in the brain of patients with AD changing from a ratio of 99:1 to 2:1.[6] This may have a favourable effect on sustained cholinesterase inhibition and subsequent disease stabilisation. On the other hand, galantamine's mechanism of action is sufficiently different from that of other AChEIs as it also acts on the nicotinic acetylcholine receptor (nAChR) sites increasing the receptor responsiveness to acetylcholine (ACh) facilitating its ionic channel opening.[7] Tacrine is rarely used nowadays because of its frequent dosing and the need to monitor liver enzymes for the development of hepatotoxicity.[2]

Nausea, vomiting, diarrhoea, dizziness, and anorexia are the most common adverse effects associated with acetylcholinesterase therapy (Table 1) and occur more frequently during dose escalation than during maintenance.[8] Gastrointestinal effects can be minimised by concurrent administration of food and the use of an anti-emetic. Insomnia, fatigue and muscle cramps occur less frequently whereas particular attention must be given in patients with bradycardia.[9] These drugs become inefficient in the treatment of severe forms of AD during which cholinergic cell population is significantly low in various areas of the brain.

The mode of action by which these drugs act is by blocking the breakdown of the neurotransmitter ACh. By inhibiting the enzyme acetylcholinesterase, the levels of the neurotransmitter at cholinergic synapses increase.

Acetylcholinesterase has also been found to promote the formation of amyloid plaques, thus inhibiting this enzyme by properly designed AChEIs might not only provide symptomatic relief but also inhibit the progression of the disease itself.[8]

Practice Points

- Alzheimer's disease should not be confounded with the mild cognitive decline that occurs in normal ageing. AD is a disease involving extensive impairment in various domains of cognition that are not characteristic of the normal ageing process.
- AD is usually accompanied by disturbance in behaviour manifesting itself in anxiety, depression, agitation, hallucinations, delusions, inappropriate behaviour and eating disorders. These neuropsychiatric disorders, which may occur in a considerable number of cases, are one of the main causes of care-giver stress.
- Health care professionals should be aware of the symptoms that characterise the disease, and if AD (or any other form of dementia) is suspected, the cases should be referred for consultation. Different forms of testing may be adopted including neuroimaging techniques as well as using assessment scales such as the Mini-Mental State Examination (MMSE).
- Community studies show that care-givers of AD patients are under significant amount of psychological stress with the majority of them ending up needing psychiatric care. Carers should be helped and provided with the necessary information of the best practices available in care-giving. In the local scene, organisations such as the Malta Dementia Society (www.maltadementiasociety.org.mt), aim to provide the best information about dementia care not only to carers and health professionals but also to the public in general.

Table 1

Characteristics of pharmacological agents commonly used in the management of AD

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

AChEI: acetylcholinesterase inhibitor; AD: Alzheimer's disease; nAChRs: nicotinic acetylcholine receptors; NMDA: N-methyl-D-aspartate

Glutamatergic-transmission modifiers

Recent research indicates that the excitatory neurotransmitter glutamate may play an important role in the neurochemistry of AD. Glutamatergic neurotransmission has been shown to be important in learning and memory and is severely disrupted in AD. Overstimulation of the NMDA receptor by glutamate leads to an overload of intracellular calcium bringing about neuronal death which is characteristic of AD and other neurodegenerative disorders.[10] Memantine (Axura®, Ebixa®), a non-competitive antagonist with moderate affinity for the NMDA receptor, appears to block pathologic neural toxicity associated with prolonged glutamate release.[11] Therapeutic doses are well tolerated and do not appear to interfere with the acquisition or processing of cognitive information in which the NMDA receptor plays an important role.[12] Memantine has been shown to improve the symptoms and reduce the rate of clinical deterioration among patients with moderate to severe AD and was approved by the FDA for this indication in October 2003. In randomised clinical trials, the drug demonstrated the ability to delay cognitive and functional decline without a significance incidence of serious adverse events.[13,14] Some studies also suggest that the efficacy of memantine in combination with AChEIs therapy may be greater than AChEIs alone significantly improving activities of daily living. This combination was also found to be well tolerated by the majority of AD patients with no serious adverse drug reactions reported.[15]

Discussion

As recently as fifteen years ago, there was no effective therapeutic agent for symptomatic relief of AD, let alone one that might halt the progression of the disease. As modest as the benefits of current treatments are, they nevertheless represent a major step in the pharmacotherapy of AD. Modest improvements mean more than symptomatic relief – they offer hope to AD patients, their physicians, and their caregivers. Therefore the latest draft guidelines issued by the UK National Institute for Clinical Excellence (NICE) recommending that AChEIs should be made available with restrictions to patients via NHS and that memantine should only be considered for clinical trials were met with strong resistance. Various AD organisations across Europe voiced their concerns about this approach, highlighting the need for NICE to assess its views and the implications that result if such guidelines are not revised. Even Alzheimer's Europe, an umbrella organisation of 28 national Alzheimer's disease associations from 24 European countries, recently issued a press release that calls for NICE to revise its preliminary recommendations for the treatment of AD and allow patients at all stages of the illness to have access to the various drug treatments irrespective of the cost.

Indeed, there is strong evidence that these drugs enhance activities of daily living, reduce behavioural disturbances, stabilise cognitive impairment, decrease caregiver stress and may delay entry into nursing homes. Apart from reducing the symptoms of the disease, these drugs may offer neuroprotection, thus stabilising the degenerative process.

The future of pharmacotherapy in the treatment of AD looks very promising. Ongoing research has not only deepened our understanding of the disease but is also suggesting a number of different avenues that may be used to develop drugs to prevent and treat AD. These include agents that block the formation of plaques and tangles by inhibiting enzymes that help in their formation. Others include chemical compounds that dissolve amyloid and fibrils which are found in the brains of AD patients.[16] Development of such drugs could also help in treating cognitive decline associated with normal ageing.

References

1. Schulz R, Mendelsohn AB, Haley WE, Mahoney D, Allen RS, Zhang S, Thompson L, Belle SH. Resources for Enhancing Alzheimer's Caregiver Health Investigators. End-of-life care and the effects of bereavement on family caregivers of persons with dementia. New England Journal of Medicine 2003; 349:1936-42.
2. Cummings JL, Cole G. Alzheimer disease. Journal of the American Medical Association 2002; 287:2335-38.
3. Scerri C. The face of dementia. BOLD – Journal of the International Institute of Ageing (United Nations, Malta) 2005;15:19-22.
4. Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD; "312" Study Group. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients [published correction appears in Neurology 2001: 57: 1942] Neurology 2001;57:481-88.
5. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Archives of Neurology 2004; 61:252-6.
6. Perry EK, Atack JR, Perry RH, Hardy JA, Dodd PR, Edwardson JA, Blessed G, Tomlinson BE, Fairbairn AF. Intralaminar neurochemical distributions in human midtemporal cortex: comparison between Alzheimer's disease and the normal. Journal of Neurochemistry 1984;42:1402-10.
7. Albuquerque EX, Alkondon M, Pereira EF, Castro NG, Schrattenholz A, Barbosa CT, Bonfante-Cabarcas R, Aracava Y, Eisenberg HM, Maelicke A. Properties of neuronal nicotinic acetylcholine receptors: pharmacological characterization and modulation of synaptic function. Journal of Pharmacology and Experimental Therapeutics 1997;280:1117-36.
8. Ellis JM. Cholinesterase inhibitors in the treatment of dementia. Journal of the American Osteopathic Association 2005;105:145-158.
9. Morganroth J, Graham S, Hartman R, Anand R. Electrocardiographic effects of rivastigmine. Journal of Clinical Pharmacology 2002;42:558-68.
10. Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. New England Journal of Medicine 1994;330:613-22.
11. Danysz W, Parsons CG, Mobius HJ. Neuroprotective and symtomalogical action of memantine relevant for Alzheimer's disease – a unified glutamatergic hypothesis on the mechanism of action. Neurotoxicity Research 2000;2:85-98.
12. Smith PF. Therapeutic N-methyl-D-aspartate receptor antagonists: will reality meet expectation? Current Opinion in Investigational Drugs 2003;4:826-32.
13. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine 2003;348:1333-41.
14. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). International Journal of Geriatric Psychiatry 1999;14:135-46.
15. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. Journal of the American Medical Association 2004;291:317-24.
16. Michaelis ML. Drugs targeting Alzheimer's disease: some things old and some things new. Journal of Pharmacology and Experimental Therapeutics 2003;304:897-904.

The Malta Dementia Society

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The patterns of illness that accompany old age have profound social and economic consequences for society as a whole and for healthcare systems in particular. Dementia is a serious, common, and rapidly growing world-wide neurological condition associated with increased healthcare utilisation. It is the major predictor of morbidity and mortality in the elderly.

Dementia is a generic term that describes chronic or progressive dysfunction of brain areas resulting in complex cognitive decline. These cognitive changes are commonly accompanied by disturbances of mood, behaviour, and personality. The condition affects about 1.5% of individuals at the age of 65 years and doubles every four years to reach about 30% at 80 years. Overall incidence increases with age and is about 1% per year and is low in men and in people of African and Asian origin. Differences in rates of dementia between developing and developed countries are difficult to explain, but might be attributable partly to the difficulties in dementia diagnosis in areas with high rates of illiteracy, and survival bias due to high death rates at all age groups. Dementia patients have a substantially shortened life expectancy with an average survival time-span being around 8 years from diagnosis.

Different forms of dementia are now distinguished; Alzheimer's disease (accounting to around 50-60 % of all cases), vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and dementia secondary to disease, such as dementia due to AIDS. Other forms of dementia include those due to vitamin deficiency, drug intoxication, alcoholism and endocrine disorders. Although the importance of accurate diagnosis is clear, this may prove to be difficult as different dementias are believed to have common underlying neuropathology. Albeit fundamental research have identified some of the neurochemical and neurobiological changes that occur in the various forms of dementia, much remains to be done in the area of disease management and the development of appropriate models of long-term care.

Extensive exploration of the possible risk factors, which has largely focused on Alzheimer's disease, has been disappointing. Age, dementia in a first-degree family member, and a history of head trauma are some of the confirmed risk factors for the disease. In vascular dementia, the main risk factors identified are age, male sex, hypertension, myocardial infarction, coronary heart disease, diabetes, smoking, hyperlipidaemia, and a history of stroke. The challenge to researchers in this field is to determine the relative importance of individual risk factors and their interactive effects. Other promising research avenues are yet to be explored. These include further development of neuroimagining and other biological marker techniques for diagnosis and monitoring, wider assessment of treatments for behavioural and psychological symptoms of dementia and strategies to support care.

The Malta Dementia Society was established in September 2004 on the occasion of World Alzheimer's Day. The society is a non-governmental organisation (NGO), intended primarily for people with dementia and their caregivers, families and friends but which also brings together healthcare professionals and other interested persons wishing to learn more

about the various aspects of dementia and its care.

The prime focus throughout the first year and a half of the society was to provide information and to raise awareness about dementia. Hence, caregivers were invited to a series of talks and video presentations discussing challenging behaviour and how to organise a daily routine for people with dementia. These activities were received with great interest and enthusiasm, and subsequently had to be repeated on several occasions. Information about the society and membership application leaflets have now been produced and a website has been set up to provide details of the society and its work. The website can be accessed at www.maltademen tiasociety.org.mt

A public lecture entitled "What is Dementia?" was presented in July 2005 by Dr Carmelo Aquilina, a Consultant in Old Age Psychiatry at the Royal Betlem Hospital, Kent, UK.

The society's first anniversary was celebrated in September 2005 with a 'Memory Walk' – a public awareness campaign that was held at Freedom Square, Valletta. Many members and friends joined together at this event, to meet the general public and to disseminate information about dementia. During this activity, members challenged the stigma that is associated with this disease by bravely parading up and down in Republic Street with banners such as "Dementia is not just getting older" and "There are 3500 people with Dementia in Malta". The 'Memory Walk' received good publicity thanks to the interest and support of the local media.

Strong international networking is maintained with Alzheimer Europe and the society has recently been elected as provisional member of Alzheimer's Disease International. The society also had discussions with the local authorities about increasing services such as establishing Specialised Day Care Centres specifically for people with dementia.

The Malta Dementia Society has collaborated with private nursing homes to deliver talks to staff on dementia care. Recently the society has teamed up with the Continuing Education Committee at St. Vincent de Paul Residence to set up a training course in Person-centred Dementia Care for staff working at this long stay residence for the elderly. It is hoped that by being involved in staff training, the society will have an influence on raising the standards of care to people with dementia in Malta.

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Upcoming Meeting

The Malta Dementia Society is organising an evening lecture:

100 years of Alzheimer's Disease

delivered by **Dr Carmelo Aquilina MD FRCPsych**
Consultant in Old Age Psychiatry, Royal Betlem Hospital, Kent, UK

Tuesday, 18 July 2006
starting at 08:00pm

At the Conference Hall, Medical School, St Luke's Hospital, Gwardamangia

A certificate of attendance for CME accreditation will be provided

This meeting is eligible for accreditation with the Malta College of Pharmacy Practice.
Proof of attendance must be produced.

Innovative medicines for Europe*

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The Joint Technology Initiative for Innovative Medicines for European Citizens is proposed within the context of the European Commission's proposals for the Seventh Framework Programme (2007-2013) and proposes clear practical paths to accelerate the development of safe and more effective approved new medicines. This will be achieved by stimulating integrated forms of co-operation in research and development, in particular through a public-private partnership (PPP), to be established especially for this purpose. This will become operational in 2007 and current calculations forecast investments of approximately €440 million per year.

Introduction

Because the European pharmaceutical industry is lagging seriously behind its competitors, mainly in the US, and seems to be particularly slow in harnessing the benefits of the revolution in biotechnology, the European Commission requested the Research Directors' Group of the European Federation of Pharmaceutical Industries' Associations (EFPIA) to identify the main barriers to innovation in Life Sciences research in Europe with the objective of establishing a new initiative for Innovative Medicines. This is because one of the major objectives of the European Union is to build the most competitive and dynamic knowledge-based economy in the world by 2010, a key element of which is to strengthen the science base in Europe. In this context, the biopharmaceutical environment is characterised particularly by its focus on science and innovation. It is therefore essential to revitalise this environment so as to make it become more competitive, not by fast-tracking the production of new compounds, but more by a root and branch review of the entire pharmaceutical R&D process. This "bench to bedside" approach would entail the development of a new "toolbox", developed through collaboration between all stakeholders (patients, industry, including the SME sector, regulators, clinical and academic researchers, etc.), that would constitute the means to streamline the R&D process and thereby ensure that patients obtain new medicines faster without compromising safety.

The development of a new drug is a long, resource intensive and complex process. The overall cost for just one compound is estimated to be €868,000,000 at prices for the year 2000.[1] The possibility of failure to reach the market by the end is high and the project may fail for many reasons at many points in its evolution. Data on product attrition rates indicate that the probability of a drug candidate passing from pre-clinical stages (first GLP toxicity study) to market is 6% or less.[2] Improving these odds depends upon a concerted research effort to overcome the perceived bottlenecks in this R&D development pathway so as to bring more efficacious and safer drugs to the market more quickly, resulting in a direct benefit for patients.

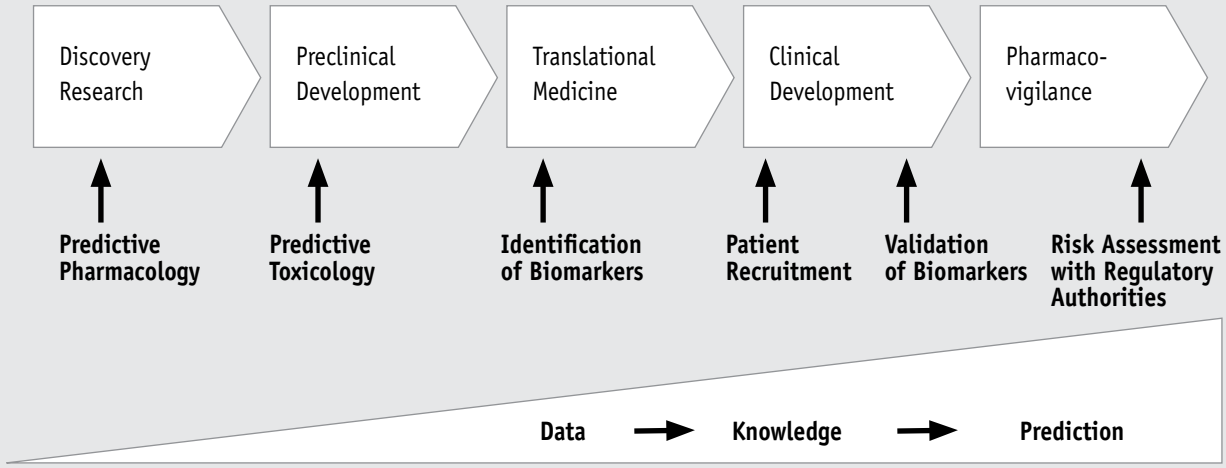
The greatest need for the pharmaceutical industry is to detect the possibility of failure at the earliest stage as possible, and it is in this context that advances in basic biomedical science within the European research community could make the greatest contribution.

At the same time, the European Commission also developed the Joint Technology Initiative concept as a means of identifying and resolving major economic, technological or societal challenges that have Research and Development aspects. These will generate effective public-private partnerships between all relevant stakeholders, whether they are companies, research institutions, the financial world and regulatory authorities at the European level to define a common research agenda which should mobilise a critical mass of - national and European - public and private resources. Joint Technology Initiatives are expected to contribute to achieving the

*The opinions expressed in this article are of the author and do not, necessarily, represent the official views of the European Commission.

Figure 1

R&D Processes in drug development



Source: EFPIA

objective for Europe of becoming "...the most competitive and dynamic knowledge-based economy in the world capable of sustainable economic growth with more and better jobs and greater social cohesion". This is referred to as the Lisbon objective, which amongst others, aims to improve the research climate in Europe in terms of better growth and competitiveness and increasing investment in R&D towards the 3% of overall European GDP. This intention was published in the Communication from the Commission entitled "Science and technology, the key to Europe's future – Guidelines for future European Union policy to support research".[3]

Clearly, a Joint Technology Initiative for Innovative Medicines was the answer.

With this in mind, industry responded by identifying 4 areas for action in agreement with key stakeholders:

- Better prediction of safety
- Better prediction of efficacy
- Knowledge management
- Education and training

Through a series of several workshops involving over 300 experts in research and development representing all stakeholder groups (academia, large pharmaceutical industries, the SME sector, regulatory agencies including the European Medicines' Agency, patient organisations and financial institutions) were consulted and came to the following conclusions on each of the above issues.

Better prediction of safety

Pre-clinical safety, or toxicological issues are responsible for 20% of the overall attrition rate for candidate medicinal products in pharmaceutical development. There is greater public and media scrutiny of pharmaceuticals and regulatory decision-making than before and a perceived overall weakness of the post-marketing surveillance system. Regulatory authorities have accordingly become more risk-averse, requiring ever broader and more restrictive risk management strategies to avoid such problems, with the need for expanded studies to quantify potential serious adverse events, even those of great rarity or scientific improbability. There is an increasing tendency for the approval of more restricted indications (with requests for increased data for broader indications) slowing down approval for marketing and delayed patient access to innovative medicines that address medical needs.

The following suggestions from the consulted experts are intended to enhance this overall process:

- Create a European Centre of Drug Safety to identify and co-ordinate research needs in safety sciences, including the development of a pan-European Safety Sciences Programme
- Establish a framework for biomarker development which will evaluate human relevance and regulatory utility
- Develop in silico methods for better prediction of safety
- Study the relevance of rodent non-genotoxic carcinogens
- Tackle intractable toxicity
- Improve healthcare provider training in detection of adverse drug reactions
- Development of databases including knowledge management tools of data analysis in pharmacovigilance
- Improve communication between patients, physicians and other healthcare providers in pharmacovigilance

Greater use will need to be made of in-silico tools and newly emerging disciplines such as toxicogenomics*, toxicoproteomics† and metabonomics‡ in

* The collection, interpretation, and storage of information about gene and protein activity in order to identify toxic substances in the environment and to help treat people at the greatest risk of diseases caused by environmental pollutants or toxicants

† The use of global protein expression technologies to understand better environmental and genetic factors, both in episodes of acute exposure to toxicants and in the long-term development of disease

‡ Used interchangeably with "metabolomics", signifying the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification

an integrated fashion so as to get a better idea and sooner of a candidate compound's chances of making it to market.

Better prediction of efficacy

A number of issues emerge as suitable and necessary for action:

Biomarkers

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". [4] They can be used as tools to understand the biology of a disease but also to understand the effects of a new drug sooner than at present. This can result in better and earlier decision-making about whether to proceed with the development of a compound, reducing late-stage and more costly attrition. This could mean benefits such as : increasing the probability of program success and reduced cycle times, matching patients with therapy; faster optimisation of therapy; improved compliance with therapy, reduced complications of therapy and disease, more efficient drug development, more efficient healthcare delivery and ultimately reduced societal healthcare burden.

Patient involvement

This is perhaps the most important part of the medicine development process and consumes over 50% of the time available. One of the major components is the patient recruitment phase which can last on average twelve months if not longer. Reducing its duration will have a substantial effect on the time needed to develop new medicines provide a competitive edge in terms of performing clinical trials. A potential means of achieving this could be through education of patients about the benefits of participating in research. They should not only be informed about the outcome of the clinical research but also be involved in the design of the study. This is important for developing a more patient-oriented approach to treatment and for their participation in an educational process involving not just them, but also carers and researchers to ensure best treatment outcomes. Issues to be resolved include the precarious nature of their funding, the establishment and maintenance of patient records and databases of information and quality of life measurements as outcomes to clinical trials that identify most closely with their experiences.

Regulatory approvals

As final judge of the risk/benefit ratio for each new application, regulatory authorities are most sensitive to public concerns about medicines as reflected in expanded requirements to outrule the possibility of serious and other adverse events. This can result in serious delays in obtaining marketing authorisations for new medicines to redress medical needs and the following items have been identified as suitable for action:

- Improved dialogue with regulators during drug development prior to regulatory approval so as to reduce requests for additional data following submission,
- Increased acceptance by regulatory authorities of biomarkers and surrogate clinical end points to clinical trials,
- Increase the involvement of other stakeholders, especially patients, in the regulatory review process,
- Develop methodologies for data collection on the risks and benefits of medicines once they are available in a real world setting,
- Ensure appropriate use of the conditional approval process for innovative new medicines with an adequate safety profile,
- Develop with regulators proposals to increase sharing of data, for example on the placebo arms of clinical trials,
- Encourage discussion on a more flexible approach to clinical trials that reflects the individual needs of particular disease areas, e.g. quality of life issues that identify closely with patient needs

Other recommendations are as follows :

- Develop better understanding of disease mechanisms,
- Develop in vitro and in vivo models predictive of clinical efficacy,
- Develop in silico simulations of disease pathology,
- Create disease-specific European Imaging Networks,
- Create disease-specific European Centres for validation of omics-based biomarkers,
- Co-ordinate the development of national patient networks,
- Form European consortia to address value demonstration,
- Develop a framework in partnership with the regulators for innovative clinical trial design and analysis.

Knowledge management

The vast sources of scientific and technical knowledge that need to be linked together under the auspices of the Joint Technology Initiative for Innovative Medicines are extremely diverse with regard to origin, availability, ownership, scientific content and many other features. This diversity, the complexity of underlying science and the means of drawing meaningful conclusions from them are also likely to increase with time.

It must therefore be asked what information is needed (and what is not needed) from such information sources, what tools are need to extract such information, how can it be analysed in such a way that will enable meaningful conclusions to be drawn from it so as to enable accurate predictions to be made that are relevant to real-life situations. The following issues need to be borne in mind.

Firstly and from the users' point of view, the knowledge management system must reflect the way those who utilise it (here : the biopharmaceutical community stakeholders as mentioned above) work together and it must integrate smoothly in their day-to-day environment. In particular, it must provide relevant, simple and intuitive access to various information sources and yet be capable of organising it according to content, allow for data to be integrated or pooled, analysed and constructed into models that reflect real-life situations. Examples include tasks as simple as identifying a clinical expert with a particular profile or as complex as pooling together the placebo arms of several clinical trials into one large pool that can serve as one virtual half of a clinical study versus a comparator product. It should also allow for issues such as virtual meetings, knowledge sharing, forums, discussions, etc., open to whole community, as well as within context-

defined sub-communities.

From the technical point of view, the key objective is to ensure seamless data integration across a broad range of heterogeneous scientific, computer and other technical resources across differing organisations and networks. Further, it should be adaptable enough to be based upon existing and emerging data representation standards and yet be able to satisfy unpredictable requirements as they emerge.

From this seemingly impossible set of requirements, only the broadest recommendations can be made and these appear to be as follows:

- To develop enhanced knowledge representation models and data exchange standards for complex systems,
- To build a core reference database of validated experimental data extracted from the literature,
- To design standards for and build an expert tool to allow the federation of local databases in a secured environment.

In principle, the required flexibility of the future platform can be met by designing a federated environment based on existing stand-alone tools, components and resources, based on open common architectural standards that can be adapted to contemporary needs and capable of dynamic reconfiguration.

Education and training

The goal of education and training activities associated with the Joint Technology Initiative for the Innovative Medicines Initiative should be to support the interdisciplinary education process essential to the bioscience sector. This entails the development of a new concept referred to as "Translational Medicne" or Translational Science", which may be defined as:

> *"...a comprehensive European-based approach aimed at a common understanding throughout all relevant scientific disciplines of the research and development steps that bring a new biochemical substance or technique (NCE, biotechnological intervention, etc.) to market as a therapeutic clinically safe and effective intervention."*

This will require the establishment of a pan-European platform responsible for the education and training of current and future professionals involved in the biopharmaceutical research and development process, including lifecycle management. It will need to be based upon existing centres of excellence within the disciplines and therefore not be a new or parallel entity.

Its main priorities will be as follows:

- To act as a central coordinating unit and an advisory education and training council
- To develop programmes for integrated medicine development, ethics committees and patient organisations,
- To develop programmes for safety scientists within pharmaceutical R&D
- To develop Regulatory Affairs-based programmes
- To develop appropriate training programmes for biostatisticians, bioinformaticians and biomedical informaticians
- To develop programmes for pharmaceutical medicine professionals

Patients and their representatives should be involved as far as possible since they can make a key contribution to the determination of what and how the professionals acquire skills and knowledge of greatest use to the public. Furthermore, there is a need for ongoing training for experts, or what is referred to as Continuous Professional Development, to keep up to date with developments in science and technology. This will entail the training of specialists to acquire knowledge from areas other than those they graduated from, e.g. business and finance training for clinical scientists working, for example in the SME sector.

Following a consultation process with relevant stakeholders, a number of gaps will need to be filled in the Education and Training process that fall under the following headings:

- Increased scientific interaction, in terms of information and personnel, between the academic world and industry and regulatory authorities on the other, to facilitate the sharing and exchange of knowledge. In most European countries this is characterised mainly by a brain-drain to industry, mostly for financial reasons.
- Safety scientists with a much broader spectrum of knowledge drawn from areas such as primary and secondary pharmacology, functional genomics, safety pharmacology, physiology, pathophysiology, physical chemistry, animal and clinical toxicology, cellular biology, biochemistry and animal physiology,
- Clinical pharmacologists, non-clinical and clinical,
- Physicians specialised in pharmaceutical medicine,
- Specialists in bioinformatics, biostatistics, systems pharmacology and physiology (in vivo whole organism), medical imaging and in-silico modelling,
- Regulatory personnel trained in disciplines arising from the Clinical Trials (GCP) Directive,[5] namely inspectors, clinical investigators, monitors, clinical research associates and members of ethics committee.
- A better understanding of the process of medicines development to be communicated to journalists, venture capitalists and the general public.

The success of these measures will depend on the support from all relevant stakeholders, especially the European biomedical industry, academia, scientific and professional societies, patient groups, regulatory bodies and the European Commission. Minimal bureaucracy will be the key to ensuring maximum flexibility and rapid action.

Legislative developments

The first and most important of these is Regulation (EC) 726/2004,[6] which governs the European Regulator, the European Medicines' Agency (EMEA) as well as the scope of the centralised marketing authorisation procedure.Up to recently, this has been a requirement for products derived from biotechnology and optional for new chemical entities. Centralised assessment is now compulsory for products intended for use in the treatment of AIDS, cancer, neurodegenerative disorders and diabetes mellitus. From May 20, 2008, this will be

extended to cover products used to treat autoimmune diseases and other immune dysfunctions, as well as viral diseases. As a consequence, many more new products will be assessed via this method.

Three new marketing authorisations have also been introduced: accelerated authorisation, compassionate use and "exceptional circumstances". The accelerated procedure (6, art. 14)[9] comprises a 150-day review as opposed to the usual 210 days and covers products, which represent a major public health or other therapeutic interest. This was first developed by the EMEA in 2001 so as to expedite the review of marketing authorisation applications for life-threatening or incapacitating disorders. In order to be evaluated under this process, a product must be indicated for a serious disease, it must be the only possible treatment and it must possess exceptionally high therapeutic benefit.

"Exceptional circumstances" (6 art. 14)[8] refers to approval for marketing of products where comprehensive information cannot be provided by the applicant (small study size due to the overall rarity of the condition e.g. in certain orphan indications), or where collecting such data would be contrary to accepted medical ethics. Such products would be available by prescription only, be subject to strict medical supervision and their package leaflets would have to be formulated in such a way as to draw attention to the fact that many particulars concerning the product are as yet unavailable or inadequate.

"Compassionate use" (6, art. 83),[7] refers to a specific provision that remains to be introduced, which will be complementary to national legislation and will provide an option to Member States who wish to receive a CHMP opinion regarding the conditions for compassionate use of a specific medicinal product which falls within the scope of the regulation.

Each of the following specific criteria should be fulfilled:

- The medicinal product is to be made available to patients with a chronically or seriously debilitating disease, or a life threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product in Europe,
- The compassionate use programme is intended for a group of patients,
- The medicinal product is either the subject of an application for a centralised marketing authorisation or is undergoing clinical trials in the European Union and/or elsewhere.

A Conditional Marketing Authorisation,[8] separate from other foregoing legal provisions, is also planned which allows for a product to be granted temporary approval under Regulation 726/2004[6] for one year only and subject to annual review by EMEA. In particular, full clinical data will have to be provided post-approval, but the applicant will still have to provide full preclinical (animal) information at the time of application as well as demonstrate a positive benefit/risk ratio of the drug. This is intended for orphan medicinal products and products intended for rapidly arising public health threats.

Pharmacovigilance and post-marketing surveillance receive greater attention. This places even greater emphasis on the continuous monitoring of the risk/benefit ratio of marketed products on an ongoing basis, taking account of all post-approval safety information. Marketing Authorisation Holders will be required to have "permanently and continuously at [their] disposal" a person appropriately qualified in pharmacovigilance. This person is responsible for managing pharmacovigilance systems and in particular, the submission of pharmacovigilance or Periodic Safety Update Reports (PSURs) to the competent authorities, which will follow a tighter timetable than before. These will have to be submitted every 6 months after approval until the product is marketed. After this has started, PSURs must be submitted every 6 months for the first two years, then once a year for another 2 years and at 3-yearly intervals thereafter. Regulatory authorities will be allowed to request a PSUR at any time at their discretion.

Directive 2004/27/EC,[9] which amends the Community Code on medicinal products for human use, foresees a number of important changes, the most important of which are as follows:

- The decentralised approval procedure, which operates alongside the mutual recognition procedure and whereby a reference member state issues its own assessment report on a proposed new product. This is circulated to other Member States, who can issue their own marketing authorisations on this basis,
- A global Marketing Authorisation, which covers all future forms, strengths, routes of administration, extensions and variations to a product. This will limit the ability of generic pharmaceutical companies from making minor changes to Marketing Authorisation Applications,
- Definition of a generic product as that with the same quantitative and qualitative composition as a reference product and that has been shown to be bioequivalent to this product. This necessarily includes all salts, esters, isomers, complexes and derivatives of that substance, unless they differ in terms of efficacy and/or safety,
- Similar biological medicines, or "biosimilars", regarded as "comparable" versions of biological drugs. This lays down a clear and firm legal pathway for their registration and is complemented by scientific guidelines from the EMEA,
- Sunset clause, whereby the marketing authorisation of product not placed on the market within three years of the date of its date of issue can be withdrawn. Companies will therefore be required to notify the regulatory authorities when they market a product,
- Market exclusivity is harmonised throughout the EU, whereby each newly approved drug benefits from eight years data exclusivity. This is extended by a further two years, during which generic versions may not be placed on the market, but can nevertheless be developed, submitted and authorised without infringing the originator's patent rights. Marketing can only commence after expiry of this period, or one year later again, if within the first eight years, a product gains a new indication deemed to be of "…significant clinical benefit in comparison with other therapies".

Small and medium-sized enterprises (SMEs)

One of the more innovative provisions of the new legislation package is the range of incentives offered to the small- and medium-sized enterprise sector operating in the field of pharmaceuticals. Under the terms of the legislation, considerable savings can be made in the seeking of various degrees of scientific advice and inspection fees at EMEA by reductions of up to 90% and the deferral of payments for such advice until after successful authorisation of products.

According to the terms of Commission Recommendation 2003/361/EC,[10] a small- or medium-sized enterprise is defined as one with fewer than 250 employees, an annual turnover not exceeding €50m and a balance sheet not exceeding €43m. A **small enterprise** has fewer than 50 employees, an annual turnover/annual balance sheet not exceeding €10m and a **micro** enterprise has less than 10 employees with an annual turnover/annual balance sheet of less than €2m.

To determine which companies are eligible for SME incentives, the EMEA will apply the definition of micro, small and medium-sized enterprises provided in this recommendation.

The main provisions of the legislation are as follows[11]:

- Administrative and procedural assistance from the SME Office at EMEA,
- Fee reductions for scientific advice, inspections and (for veterinary medicines) establishment of maximum residue limits,
- Fee exemptions for certain administrative services of the EMEA,
- Deferral of the fee payable for an application for marketing authorisation or related inspection,
- Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful,
- Assistance with translations of the product information documents submitted in the application for marketing authorisation.

A responsible and especially dedicated office has been established at the EMEA for the submission of requests for designation of SME status and to answer further queries.[12] A comprehensive guide has been published giving further information. [13]

Seventh framework programme

It is intended that the Joint Technology Initiative for Innovative Medicines will be an integral and yet autonomous part of the Seventh Research Framework Programme.[14] In this, collaborative research will constitute the bulk and the core of EU research funding. The objective is to establish, in the major fields of advancement of knowledge, excellent research projects and networks able to attract researchers and investments from Europe and the entire world.

Within the health domain, the primary concern remains to improve the health of European citizens while at the same time to increase the competitiveness of European health-related industries and businesses. Emphasis will be put on bringing the fruits of research to market as soon as possible in the form of safe and effective clinical applications, new therapies, methods for health promotion and prevention, diagnostic tools and technologies, as well as sustainable and efficient healthcare systems.

Activities extend to three 3 main areas :

- Biotechnology, generic tools and technologies for human health, including research in molecular screening, diagnostics, alternatives to animal testing
- Translating research for human health, including ageing, brain diseases, infectious diseases and major diseases
- Optimising the delivery of healthcare to European citizens, comprising more efficient use of health care interventions

All activities will be carried out in pursuit of the general objectives described in Article 163 of the Treaty in contributing towards the creation of a knowledge-based society, and to build on a European Research Area for all European citizens.

References

1. DiMasi JA Hansen RW Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of Health Economics 2003 Mar;22(2):151-85
2. EFPIA, The Pharmaceutical Industry in Figures, Key Data, 2005 update.
3. Science and technology, the key to Europe's future – Guidelines for future European Union policy to support research", COM (2004) 353, 16/06/2004.
4. Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," Clinical Pharm. & Therapeutics, vol. 69, N. 3, March 2001
5. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Official Journal of the European Communities 1.5.2001 L121/34
6. Regulation EC No.726/2004 Of The European Parliament And Of The Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Official Journal of the European Union L 136/1, 31.3.2004
7. Committee For Medicinal Products For Human Use (CHMP) Guideline on Compassionate Use of Medicinal Products, pursuant to Article 83 of Regulation (EC) No 726/2004, EMEA/27170/2006/ Draft, London 20 March 2006.
8. European Commission. Draft Commission Regulation on the Conditional Marketing Authorisation for Medicinal Products Falling Within the Scope of Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004. (EC, Brussels, Belgium, November 9, 2004).
9. Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, Official Journal of the European Union L 136, 30.04.2004
10. COMMISSION RECOMMENDATION of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (notified under document number C(2003) 1422) Official Journal of the European Union 20.5.2003 L 124/36-41.
11. COMMISSION REGULATION (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises, Official Journal of the European Union 16.12.2005 L 329/4-7.
12. http://www.emea.eu.int/SME/SMEoverview.htm
13. SME definition, User guide and model declaration, European Commission, EN NB-60-04-773-EN-C 92-89 4-7909-4.
14. Proposal for a Decision of the European Parliament and of the Council concerning the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007 to 2013), Brussels, 6.4.2005, COM(2005) 119 final.

The Pharmacy Council

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The Health Care Professions Act (HCPA) determines the organisation, roles and responsibilities of the Pharmacy Council of Malta. The Council's work affects all members of the pharmacy profession in all areas of practice as well as beneficiaries or stakeholders of the professional services it relates to.

The Pharmacy Council addresses issues related to both pharmacists and pharmacy technicians. A general outline and description of The Council's current activities and the challenges it faces will be discussed as well as its vision for the future of the profession and its practice.

Functions of the Pharmacy Council

As members of a regulated profession, pharmacists need to meet certain qualification and experience criteria that attest to having the necessary expertise to practise. In Malta, the criteria to be utilised for licensing a Pharmacist are defined via Articles 13 and 14 of the Health Care Professions Act (HCPA).

Once licensed by the competent authority, a Pharmacist becomes authorised to practise within the unique legal, professional and ethical rules within the national territory.

This activity represents the ***core functions*** of the Council. The Council primarily ensures that persons wishing to be licensed as pharmacists meet the necessary requirements. A Register of such persons is kept and maintained by the Council. Consequently the Council must ensure that at all times such practice meets strict professional and ethical standards and if not, it is empowered to take strict disciplinary measures to protect the reputation of the profession and safeguard patients against the risk of misconduct or even malpractice.

To do so, the Council needs to have the necessary ***legal mandate*** and authority to act in this manner. This is afforded to it via the HCPA that defines its composition and its roles, functions, operational parameters and general procedures. The HCPA also defines the limits of authority of the Council to regulate the profession and its practice by defining those professions it regulates and the tools afforded to it to regulate these professions (reference should be made to Part III of the Act).

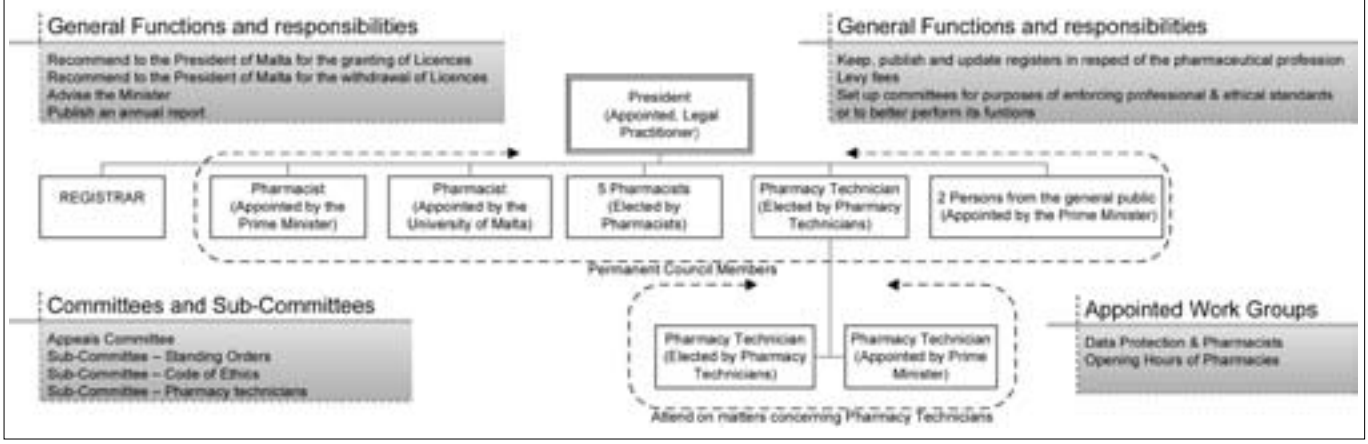
The composition of the Council

The HCPA (Article 15) determines that the Council be composed of 11 permanent members and two Pharmacy Technicians that may attend when any matter concerning Pharmacy Technicians is discussed. Of the permanent members, six are elected by the profession and five are appointed by Government or other institutions (Figure 1). The only full-time and remunerated staff member is the Registrar who is also responsible for the day-to-day administration of the Council's affairs.

The scope of this composition is to maintain a balance between ensuring that the profession may harbour and apply the principle of self-regulation while at the same time ensuring adequate representation of civil society, and the beneficiary of the profession's activities – the patient. Moreover, the term of office of all Council members is of three years. This gives the Council a higher degree of stability thus allowing it more space and time to act in the longer term and facilitates for a higher degree of continuity. All this should help instil confidence in the activity of the Council as being representative of the profession and its beneficiaries, acting in a planned, coherent and transparent manner and most of all, being accountable for its actions.

Figure 1

The composition and general roles and functions of the Pharmacy Council



Council activities

The Council has only been recently established and takes over and builds on the experience and achievements of the Pharmacy Board. The activities of the Pharmacy Council over the past two years are illustrated in the annual reports for 2004 and 2005. The first priority of the Council was to ensure it has adequate and updated legal tools to carry out its functions. For this purpose it established a sub-committee to update the Council's standing orders, that define how the Council executes its roles and functions.

Another sub-committee was appointed to update the Code of Ethics. This has now been presented to the public for their views before its publication (http://www.sahha.gov.mt/showdoc.aspx?id=89&filesource=4&file=drftcodeofet_pharm.pdf). Consequently, more detailed Codes of Practice that give the principles enshrined in the Code of Ethics a more practical interpretation designed to fit the specific area of practice (e.g. Community Pharmacy) will be developed together with practitioners in the specific area of practice.

Where it was deemed relevant, the Council has appointed and will continue to appoint members of the profession and other experts to its sub-committees. This expands the interpretation of the principle of self-regulation by increasing practitioner participation in the definition of the rules that determine and define the practice of Pharmacy in Malta. It also helps ensure that the Council's recommendations and activities better reflect current scientific knowledge, practice and realities.

Another priority is the maintenance of the Registers held by the Council. In this respect, the main challenges came from new legislation (specifically, the HCPA and the Data Protection Act) and from the information requirements demanded of the Council by national and EU institutions, hence the detailed questionnaire sent to all registered practitioners last year.

The Pharmacy Council is also a consultative body on new national and EU legislation and matters affecting the pharmaceutical profession, pharmacists and medicines. The Pharmacy Council is also active in the Forum Malta fl-Ewropa and makes submissions and recommendations in this respect.

Importantly, EU membership has brought about a new reality for the Council that now has to facilitate the exercise of EU nationals' (including Maltese persons) right for freedom of movement and establishment. Unfortunately, experience is teaching us that to keep with the demands of this role and responsibility is no easy task. The Council's very limited human and financial resources make it difficult to match those of its European counterparts especially in areas of disagreement. It is also difficult to be active members of the EU and its numerous institutions and decision-making fora. Despite our local limitations, the Council is striving to be effective. It is undertaking initiatives that will help it secure EU funds and support aimed specifically at addressing these lacunae and limitations especially in terms of investment needed towards institution-building and EU participation.

The Council is also actively seeking to represent and protect the professions it regulates by also intervening with the authorities on issues and matters that concern the profession and patients but are not under its direct jurisdiction. Examples of this are proposals or opinions presented with respect to the list of essential equipment to be kept in a pharmacy, pharmacy opening hours, waiting room charges, the 'avian flu pandemic' and the National Formulary. In most cases, the proposals were drafted with the assistance of a sub-committee comprised of practitioners of relevant expertise.

The Council is taking initiatives to promote the important role in society of its regulated practitioners. One initiative is the issue of Council-registered pharmacist identification tags. In collaboration with the Medicines Authority it will be obligatory to wear this when practising in the Community. This will help promote the profession by helping patients to identify in the pharmacy that professional that may provide them with appropriate advice and guidance on their medicine and health related issues.

Together with the Office of the Data Commissioner the Council is developing

and will subsequently publish guidelines that will help regulated practitioners better understand the Data Protection Act and ensure conformity to the Act in their practice.

With the introduction of nominal registration fees, the Council is addressing its obligations to become not only a functionally but also a financially autonomous public entity. The Council now has its own funds and is making investments that will help it be of better service to the profession and the community it serves.

The Council's vision for the future

This autonomy will help the Council look ahead and act with confidence and certainty to achieve its vision. In this respect, the Council is taking action to bring under its wing all areas of practice within the medicines chain. It has already responded and made its proposals in respect of Qualified Persons. Similar initiatives are planned for Responsible Persons and medical representation.

Secondly, the Council is promoting collaboration and co-ordination between stakeholders in the field. It is in fact developing a more appropriate website, has opened the draft Code of Ethics to public consultation, met with consumer associations, the Chamber of Pharmacists, the Malta College of Pharmacy Practice, the GRTU and government entities like the Medicines Authority and the Office of the Data Protection Commissioner. All these discussions are bearing fruit.

Conclusion

Through our leadership, activity and actions the Council aims to establish an appropriately defined and regulated environment that increases the prestige and public confidence in those professions regulated by the Council and which allows them to provide the most professional and ethical service that our community deserves.

I am a Pharmacist

I am a specialist in medications
I supply medicines and pharmaceuticals to those who need them.
I prepare and compound special dosage forms.
I control the storage and preservation of all medications in my care.

I am a custodian of medical information
My library is a ready source of drug knowledge.
My files contain thousands of specific drug names
and tens of thousands of facts about them.
My records include the medication and health history of entire families.
My journals and meetings report advances in pharmacy from around the world.

I am a companion of the physician
I am a partner in the case of every patient who takes any kind of medication.
I am a consultant on the merits of different therapeutic agents.
I am the connecting link between physician and patient
and the final check on the safety of medicines.

I am a counselor to the patient
I help the patient understand the proper use of prescription medication.
I assist in the patient's choice of non-prescription drugs
or in the decision to consult a physician.
I advice the patient on matters of prescription storage and potency.

I am a guardian of the public health
My pharmacy is a center for health-care information.
I encourage and promote sound personal health practices.
My services are available to all at all times.

This is my calling. This is my pride.

Anon

Source:
Pharmaceutical Dosage Forms
and Drug Delivery Systems
Howard C. Ansel, Nicholas
G. Popovich and Loyd V. Allen Jr.
Sixth edition, 1995
Publisher: Williams & Wilkins,
Malvern PA (USA)

Osteoporosis: bare bone facts

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Keywords: osteoporosis, predisposing factors, treatment, advice to patients

Osteoporosis has become increasingly recognised as a major health care problem as it is the cause of more than 2.3 million fractures annually in Europe and USA alone. These fractures place an enormous medical and personal toll on the individual and a major economic burden on the nation. Osteoporosis can be prevented, and once diagnosed, can be treated. The aim of prevention and treatment of osteoporosis is to prevent the occurrence of future fractures. Lifestyle changes should be encouraged in high risk patients. Pharmacological interventions include the bisphosphonates, selective oestrogen receptor modulators, hormone replacement therapy (HRT), calcitonin, teriparatide, calcium and vitamin D supplements, and calcitriol.

Osteoporosis is a silent systemic skeletal disease which commonly leads to fractures that can occur in the absence of trauma or following minimal trauma.[1] Fractures commonly associated with this disorder are those involving the thoracic and lumbar spine, distal radius and proximal femur.[2]

Osteoporosis was defined by the World Health Organisation as "A disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk".[3]

Classification of osteoporosis

Osteoporosis can be defined as being either primary or secondary in origin.[4] Primary osteoporosis is said to exist where there are no other contributory diseases present. In women, 70% of all osteoporosis cases are defined as being primary, although the vast majority of these are due to post-menopausal oestrogen deficiency.[5] In men, however, only 46% of osteoporosis sufferers have no known predisposing illness but a further 16% are known to have hypogonadism.[5]

Secondary osteoporosis is said to exist where a pre-existing disease can be identified as leading to the development of osteoporosis. However, in some cases this may be iatrogenic i.e. through drug administration.[4] Table 1 gives a summary of causes of secondary osteoporosis.

Factors affecting bone mineral density

- **Physical activity:** The first evidence of an association between physical activity and bone mineral density (BMD) came from studies of the effect of inactivity on bones, particularly the osteopenic effects of weightlessness in astronauts during space flights.[6] Physical activity has also been recognised as influencing the attainment of peak bone mass in childhood and adolescence.[6]

- **Calcium** is one of the most important constituents of bone and adequate intake and absorption are required to ensure that enough calcium is available to fulfil the needs of the growing skeleton. The absorption of calcium from the diet relies on two mechanisms. With a high calcium intake most calcium is absorbed passively from the gut. However, with low intakes, calcium absorption relies on an active transport system in the intestinal mucosa which is vitamin D dependent. Therefore a low calcium intake combined with a low vitamin D availability would greatly impair the amount of calcium available for bone formation. The maximal effect of a calcium supplement appears to occur with a dosage of approximately 1000mg per day which should take into account dietary intake.[6] High calcium intake is needed in childhood to achieve the optimum peak bone mass and therefore help prevent subsequent osteoporosis.[5]

- **Vitamin D** is necessary for the normal absorption of calcium from the intestine, and hence a deficiency of this vitamin is a risk factor for osteoporosis. Low vitamin D status is attributed to low dietary intake, decreased skin exposure to the sun, or impaired synthesis of vitamin D in the skin.[6]

- **Caffeine:** dietary caffeine induces a negative calcium balance through increased urinary loss.[6]

- **Smoking:** the adverse effect of smoking on bone is likely to be mediated through changes in endogenous oestrogen metabolism; oestrogen production is decreased and metabolic clearance has been reported to be increased in smokers, but this has not been confirmed in all studies.[6] In addition, smoking is known to lead to an earlier menopause and hence to earlier post-menopausal status and earlier onset of the phase of rapid bone loss.[5] Smoking has also been associated with lower BMD in males.

- **Alcohol** is directly toxic to bone as it reduces bone cell proliferation and activity. As well as having a direct effect on bone, heavy alcohol consumption is also associated with poor nutrition, decreased calcium intake, reduced mobility and low vitamin D, all of which will have a compounding effect on reducing bone mass through their own individual actions.[5]

- **Gynaecologic variables**, such as oral contraceptive use, parity, breastfeeding, age at menarche, and menstrual cycle irregularities have all been associated with BMD.[6] Women with late onset of menarche have been reported to have significantly reduced peak bone mass and increased fracture risk. The effects on bone of oligomenorrhea and periods of amenorrhea have been documented mainly in cross-sectional studies which reported lower values for BMD than in control populations.[6]

- **Genetic factors** are clearly important in the determination of peak bone mass and this appears to be the stage at which they exert most effect, but they could also be determinants of fracture risk which are in part independent of BMD.[5]

- **Thin body type:** it is well recognised that thin individuals have lower bone mineral density than heavier individuals, and there may be multiple reasons for this.[5] Increased weight will put more stress on the skeleton and help maintain BMD in a similar way to exercise.

- **Race:** Afro-Carribean women have a higher BMD than white women at all ages due to a higher peak bone mass and slower rate of loss. White women have a 2.5-fold greater risk of getting osteoporosis.[3]

Table 1

Causes of secondary osteoporosis[4,5]

Endocrine abnormalities
Hyperthyroidism
Hyperparathyroidism
Cushing's syndrome
Diabetes mellitus
Hypogonadism (in males)

Drugs
Glucocorticoids
Anticonvulsants
Heparin therapy (long term)

Neoplastic conditions
Multiple myeloma
Bone metastases

Others
Anorexia nervosa
Alcoholism
Chronic liver disease
Inflammatory bowel disease
Rheumatoid arthritis
Renal disease
Vitamin D deficiency
Malabsorption syndromes:
- Post gastrectomy
- Coeliac disease

Who should be treated?

If drugs were 100% efficacious, 100% safe and cost-free, and patients were 100% compliant, the answer would be to treat everyone and early.[2] Knowledge on an individual's absolute risk is central to making treatment decisions. The imperative to intervene increases with advancing age, lower BMD and previous fracture, as each of these contributes independently to fracture risk.

Most therapeutic agents currently used to treat osteoporosis inhibit bone resorption. Two exceptions include teriparatide, which promotes bone formation, and strontium ranelate, which has a dual mode of action.[7] Selection should take into consideration the evidence for efficacy of different interventions, the long term effects of agents and the differing modes of action.

Calcitriol

Calcitriol has been shown to decrease bone loss in women with osteoporosis, but study results differ.[7] A decrease in vertebral fracture frequency has been demonstrated but no protective effect has been shown for hip fracture.[8] Calcitriol is licensed in the UK for the treatment of postmenopausal osteoporosis.[9]

Table 2

Advice and patient education

Advice to patients:
- Eat a healthy balanced diet with adequate calcium and Vitamin D intake
- Avoid high alcohol intake
- Eat a diet rich in fruits and vegetables
- Do not smoke
- Keep an active lifestyle, including weight bearing exercise
- Keep a healthy weight for height
- Maintain a good posture

Educate patients on:
- The dangers of falling, including information about periods of greatest risk i.e. rising too quickly after eating or resting
- Awareness and reduction of home hazards – increasing home safety includes optimal lighting, elimination of slippery or hazardous home surfaces and ensuring adequate hand supports

Calcitonin

Calcitonin is a peptide hormone with antiresorptive properties in bone.[10] It decreases further bone loss at vertebral and femoral sites in patients with documented osteoporosis but has a questionable effect on fracture frequency.[11] Calcitonin produces an analgesic effect with respect to bone pain.[12] The increase in bone density resulting from this therapy is significantly less than that achieved by alendronate or oestrogen, and may be limited to the spine, but it still has value in reducing the risk of fracture.[11] It can be administered either by subcutaneous injection, intramuscular injection or as a nasal spray.[7,9]

Strontium ranelate

Strontium ranelate stimulates bone formation and reduces bone resorption and is the first of a new class of osteoporotic treatments. In the UK it is licensed for the treatment of postmenopausal osteoporosis.[7] The Scottish Medicines Consortium has advised (July 2005) that strontium ranelate should be restricted to use when bisphosphonates are contra-indicated or not tolerated and then only in women aged over 75 years with a previous fracture and low bone mineral density or in other women at equivalent risk.[9] Avoidance of calcium-containing foods and tablets within two hours of taking the strontium ranelate is important to avoid drug interactions and loss of efficacy.[13] Clinical trials did not provide evidence of an increased incidence of upper gastrointestinal side effects and the main side effect of diarrhoea is reported to be short-lived. An increased risk for thrombosis has been noted which is being investigated by the manufacturers.[7]

Teriparatide

Teriparatide, a recombinant, fragment of parathyroid hormone, has been shown to stimulate new bone formation by direct effect on osteoblasts.[14, 15] It is the first licensed anabolic drug used to reduce the risk of vertebral fractures in established osteoporosis.[7] Teriparatide is available as a subcutaneous injection[9] and is usually used when the patient is resistant to other antiosteoporotic treatments.[9, 17]

Selective oestrogen receptor modulators

Raloxifene is a nonsteroidal benzothiophene compound[8] with tissue-specific oestrogen agonist and antagonist actions.[8,, 16] It has beneficial effects on the skeleton and blood lipid levels, but does not stimulate breast or uterine tissue.[16] The drug has been shown to increase the risk of venous thromboembolism to the same degree as oestrogen.[7] One advantage of raloxifene is its antagonistic action in the endometrium – when taken over two years, raloxifene did not affect endometrial depth.[7]

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate which adsorb onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.[9] Nitrogen-containing bisphosphonates, such as alendronate, risedronate and pamidronate, may suppress bone resorption by a different mechanism from that of etidronate or clodronate, which do not contain nitrogen.[16] Bisphosphonates have an important role in the prophylaxis and treatment of osteoporosis and corticosteroid-induced osteoporosis; alendronic acid or risedronate sodium are considered the drugs of choice for these conditions, but disodium etidronate may be considered if these drugs are unsuitable or not tolerated.[9] Bisphosphonates are poorly absorbed by the intestine and their absorption is further reduced by food, especially if it contains calcium. They should, therefore, be taken in the fasting state 30 to 60 minutes before a meal and only with water.[3]

It is important to note that bisphosphonates do not work optimally when there is underlying vitamin D deficiency.[7]

Table 3

Treatment of Osteoporosis[9,13, 18-22]*

Post-menopausal osteoporosis	Glucocorticoid-induced osteoporosis
1st line ***Oral Bisphosphonates***	
Alendronate 10mg daily or 70mg once weekly	*Alendronate* For postmenopausal women not on HRT: 10mg once daily Other patients: 5mg once daily
Etidronate 90-day cycles of 400mg disodium etidronate for 14 days followed by 76 days of 500mg elemental calcium	
Risedronate 5mg daily or 35mg weekly	*Risedronate* 5mg daily
2nd line	
Strontium ranelate - 2g daily	*HRT* (dose depends on preparation used)
3rd line *Raloxifene* - 60mg daily	

* A number of other drugs which are available on the local market are commonly used for the treatment of osteoporosis. However, since their use is unlicensed for the treatment of postmenopausal and glucocorticoid-induced osteoporosis such drugs were not mentioned in this table.

Oestrogens

Maintaining adequate oestrogen levels remains the most important way of maintaining adequate bone density in women.[11] Evidence indicates that oestrogens reduce bone turnover and prevent bone loss.[16] Calcium supplementation amplifies this effect. Oestrogen receptors have been demonstrated on osteoblasts and on other cells in the bone microenvironment but the precise mechanism of oestrogen action is still unclear.[16] The risks and benefits of oestrogen combined with progestogen treatment are complex and require the individual assessment of each woman.[3] The CSM has advised that Hormone Replacement Therapy should not be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years, but bone loss resumes (possibly at an accelerated rate) on stopping HRT.[9]

Conclusion

Many patients are not being given appropriate information about prevention, are not having appropriate testing to diagnose osteoporosis or establish osteoporosis risk, and once diagnosed too many patients are not being prescribed effective therapies.[1] Table 2 gives a summary of the appropriate advice and education which should be given to patients.

The prevention of osteoporosis is life-long. The risk is reduced if a healthy lifestyle is maintained, whilst those at risk of developing osteoporosis should be targeted and given the correct preventive treatment. Once osteoporosis is diagnosed following a fracture, treatment should be given. Choice of therapy should be made following a full discussion with the patient, in which the benefits and side-effects are outlined, so that the patient can make an informed choice about his/her treatment.

Practice Points

- The prevention of osteoporosis begins with the acquisition of optimal bone mass during growth. Anything hindering the acquisition of bone mass such as malnutrition, should be identified and dealt with during childhood
- Lifestyle advice should be provided for optimal bone health to those at risk of osteoporosis
- When present, secondary causes of osteoporosis should be treated/managed
- The most appropriate treatment of osteoporosis for each particular patient should be determined
- Strategies which aim to reduce the risk of falls should be explored

References

1. National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Washington (DC): National Osteoporosis Foundation; 2003 Apr. 37 p.
2. Chisholm D, Zajac J D. Treatemnt of osteoporosis: why, whom, when and how to treat. Med J Aust 2004; 180(6): 298-303.
3. Scottish Intercollegiate Guidelines Network Management of Osteoporosis June 2003
4. Tanna N Osteoporosis and its prevention. Pharm J 2005 vol 275 521-524.
5. Liggett NW, Reid DM. The incidence, epidemiology and aetiology of osteoporosis. Hospital Pharmacist 2000 Vol 7 No 3 62-68.
6. Guthrie JR, Dennerstein L, Wark JD. Risk Factors for osteoporosis: A review. Medscape
7. Tanna N. Osteoporosis and its treatment. Pharm J 2005; 275:581-584.
8. Christodoulou C, Cooper C. What is osteoporosis? Postgrad Med J 2003; 79: 133-138.
9. Mehta D. (Ed.) British National Formulary 51st Edition, March 2006. Available at: http://www.bnf.org.uk (Last accessed 10th May, 2006).
10. Micromedex® Healthcare Series, (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com (cited: 05/03/2006).
11. South-Paul J. Osteoporosis: Part II. Nonpharmacologic and Pharmacologic Treatment. Am Fam Physician 2001; 63(6):1121-8.
12. American Medical Association (AMA). Osteoporosis Management: The online series. Accessed at http://www.ama-cmeonline.com/osteo_mgmt/.
13. Servier Laboratories Ltd. Protelos® (strontium ranelate) Summary of Product Characteristics November 2004. Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=15410 (Last accessed 10th May, 2006).
14. National Institute for Clinical Excellence. Bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Technology Appraisal 87. London: National Institute for Clinical Excellence; January 2005.
15. Reginster JV. New agents for the treatment of osteoporosis. Medscape January 2003.
16. World Health Organisation (WHO). Prevention and Management of Osteoporosis. WHO Technical Report Series 2003.
17. De Gabriele P. Risk factor identification and prevention of osteoporosis in the primary care setting. Malta Medical Journal 2006; 18(01): 40-45.
18. PRODIGY Knowledge (2006) Osteoporosis-treatment and prevention of fragility fractures. Sowerby Centre for Health Informatics at Newcastle Ltd. (SCHIN) http://www.prodigy.nhs.uk/osteoporosis_treatment/view_whole_guidance [Accessed 25th May, 2006]
19. MSD Fosamax® (alendronate sodium) Summary of Product Characteristics March 2006. Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed 29th May, 2006).
20. Procter and Gamble Pharmaceuticals UK Limited. Actonel® (risedronate sodium) Summary of Product Characteristics February 2005. Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed on 29th May, 2006).
21. Procter and Gamble Pharmaceuticals UK Limited. Didronel PMO® (etidronate disodium) Summary of Product Characteristics July 2003 Accessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed on 29th May, 2006).
22. Eli Lilly and Company Limited. Evista® (raloxifene hydrochloride) Summary of Product Characteristics. June 2004. Acessed at http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1292 (Last accessed on 29th May, 2006).

Press Release

Issued – Friday 5 May 2006, London, UK & Basel, Switzerland

In a New Study *Rotarix™* Offers 96% Protection Against Severe Rotavirus Gastroenteritis and Prevents 100% of Rotavirus-Associated Hospitalisations

New data confirms benefit of vaccination against rotavirus in Europe

Data from a new study announced today at ESPID (European Society for Paediatric Infectious Diseases) shows that *Rotarix*™, the first oral rotavirus vaccine available to children in Europe, protect is against 96% of severe rotavirus gastroenteritis (RVGE) cases and prevents 100% of hospitalisations due to rotavirus-induced gastroenteritis in a European setting[1].

Rotavirus is the most common cause of severe acute gastroenteritis in infants and young children,[2,3] causing an estimated 3.6 million episodes of RVGE annually among the 23.6 million children aged under 5 years in the EU. Each year rotavirus causes the hospitalisation of approximately 87,000 babies and over 700,000 visits to the doctor[4].

Principal Investigator, Prof. Dr. Timo Vesikari, University of Tampere, Finland, commented, "These data are very encouraging and show that very young infants can be effectively protected against the highly contagious rotavirus with *Rotarix*™. With prevention of all hospitalisations due to RVGE demonstrated in the trial, the inclusion of a vaccination against rotavirus into routine vaccination schedules across Europe would significantly reduce the burden on healthcare resources. This is a particular problem in winter when rotavirus outbreaks are most common."

Rotarix™ is a two-dose, oral vaccine that can be administered at approximately two and three months of age (the first dose can be given as early as 6 weeks and the second dose before 6 months of age). The vaccine offers early protection against RVGE before the peak incidence of disease at 6-24 months of age.[5,6] The double-blind, placebo-controlled phase III trial, was conducted in six European countries (Czech Republic, Finland, France, Germany, Italy and Spain).

High efficacy of the vaccine, tested from two weeks following the second dose, was shown against any severity of RVGE illness (87%) and against severe RVGE caused by the most common circulating strains of rotavirus – G1 (96%), G3 (100%), G4 (100%) and the globally emerging G9 strain (95%)[1]. Evidence was also observed of a cross-protective trend against severe RVGE due to the G2 strain (75%). Additionally, the study provides further evidence that the rotavirus vaccine can be safely co-administered with other routine childhood vaccinations, including the conjugated meningococcal C and pneumococcal vaccines, without impairing the immune response of the co-administered antigens.[7,8,9]

Hospitalisations associated with rotavirus present a significant burden in Europe, with RVGE accounting for up to 58% of hospitalisations due to diarrhoea and vomiting.[10] In this trial, *Rotarix*™ offered 100% protection against hospitalisation due to RVGE independent of the rotavirus strain. The vaccine also showed a 75% efficacy against hospitalisation due to gastroenteritis of any cause[1].

The vaccine's safety profile has been highlighted in a recent trial. It demonstrated that *Rotarix™* has no attributable risk for intussusception, a complication which was observed with a previously marketed vaccine[5].

The high infectivity of rotavirus makes it difficult to control the spread of the disease. Therefore, vaccination is recognised as the only control measure to have a significant impact on the incidence of severe RVGE and is considered the optimum first line strategy for disease prevention[11,12].

About Rotarix

Rotarix™ has been developed by GlaxoSmithKline Biologicals since 1997. *Rotarix*™ derives from the parent strain 89-12, which was originally developed by Dr Richard Ward at the Children's Hospital of Cincinnati, and which was in-licensed from AVANT Immunotherapeutics. It is the first licensed attenuated human rotavirus oral vaccine conferring protection against severe rotavirus diarrhoea with data also showing efficacy against emergent strains. The vaccine is highly immunogenic and can be co-administered with all major infant vaccinations including oral polio vaccine[13].

The European Commission granted approval of *Rotarix*™ in the European Union in February 2006, allowing active vaccination of infants from the age of 6 weeks. *Rotarix*™ is the first vaccine available to children in Europe for the prevention of gastroenteritis caused by rotavirus. In addition to the European licence, over 35 licences have been granted worldwide (16 Latin American countries including Brazil; Philippines and Singapore being the first Asian countries; with Australia being one of the more recent countries), and 1.4million doses of the vaccine have been distributed since it was first launched in Mexico in 2005. Furthermore, *Rotarix*™ has been filed for approval in 75 countries. In the United States, GSK is in late stage development discussions with the FDA regarding licensure of *Rotarix*™ for the US market.

Recently, Brazil, Panama and Venezuela included the rotavirus vaccine in their national official vaccination calendars. As part of the government's paediatric immunization program, vaccination with *Rotarix*™ will be available free at public health clinics in those countries.

This vaccine is now available in Malta.

References

1. Vesikari T, et al. Human Rotavirus Vaccine *Rotarix*™ (RIX4414) is Highly Efficacious in Europe. Oral presentation at ESPID annual meeting, May 2006
2. Bresee J et al. Generic protocol for hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children. World Health Organisation, November 2002. Available at www.who.int/vaccines-documents/. Accessed in December 2005.
3. Kapikian A, Chanock R. Rotaviruses. In: Fields B et al, editors. Fields Virology, 3rd ed. Philidelphia: Lipincott-Raven Publishers; 1996. p.1657–1708
4. Soriano-Gabarro M, et al. Burden of rotavirus disease in European countries. Paed Infect Dis J 2006:25 (1):S7-S11
5. Ruiz-Palacios GM, et al. Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis. N Engl J Med 2006;354:(1):11-22
6. Linhares AC et al. Rotavirus vaccines and vaccination in Latin America. Pan Am J Public Health 2000;8 (5):305-331
7. Vesikari T, et al. *Rotarix*™ (RIX4414), an oral Human Rotavirus Vaccine, Is Highly Immunogenic when Co-administered with Diptheria-Tetanus-Pertusussis (DTPa)-combined Vaccines in Healthy Infants from Europe. Poster presentation at ESPID annual meeting, May 2006
8. Schuster V et al. *Rotarix*™ (RIX4414), an oral Human Rotavirus Vaccine, Is Highly Immunogenic when Co-administered with a *Streptococcus pneumoniae* Conjugate Vaccine (*Prevenar*™) in Healthy Infants from France and Germany. Poster presentation at ESPID annual meeting, May 2006
9. Tejedor JC et al. *Rotarix*™ (RIX4414), an oral Human Rotavirus Vaccine, Is Highly Immunogenic when Co-administered with a *Neisseria meningitidis* Serogroup C Vaccines (*Meningitec*™) in Healthy Infants from Spain. Poster presentation at ESPID annual meeting, May 2006
10. de Wit MA, et al. Hospital admissions for rotavirus infection in the Netherlands Clin Infect Dis 2000;31:698–704
11. Dennehy PH. Transmission of rotavirus and other enteric pathogens in the home. Pediatr infect Dis J 2000;19(10 Suppl):S103-5
12. Parashar UD, et al. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9:565-72
13. Steele AD. Et al. Concomitant administration of live attenuated oral rotavirus vaccine (RIX4414) with poliovirus vaccines in African infants. Poster presented at ESPID annual meeting, May 2005

The complexity of treatment with warfarin

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Maintaining a patient within a therapeutic international normalized ratio (INR) is the main aim of treatment with warfarin. Anticoagulation above or below the therapeutic window may result in bleeding or thrombosis respectively. This is made more complex by the numerous factors that may affect warfarin management including other drugs, diet and disease. This review aims to highlight factors that may affect therapy with oral anticoagulants (Figure 1). A sound knowledge of such factors ensures safe administration of warfarin.

Warfarin and other medications

There may be two forms of interactions between warfarin and other drugs:[1]

a) Pharmacokinetic interactions
which include:

- Alteration in absorption: This may involve an alteration in absorption of either vitamin K or warfarin. It may include alteration of gut flora causing reduced availability of vitamin K (eg some broad spectrum antibiotics)[2], or binding with warfarin resulting in reduced absorption (eg cholestyramine or colestipol).[2,3] In the latter case, separating the two drugs by 4-6 hours may help overcome this interaction.[3]
- Interference with warfarin metabolism: Drugs may inhibit or induce cytochrome (CYP) enzymes involved in the metabolism of warfarin and may therefore alter the plasma concentrations of warfarin. Warfarin is a racemic mixture with the (S) form being five times more potent than the (R) form.[4] Hepatic metabolism involves separate pathways, and drugs may exhibit stereoselectivity by inhibiting one form but not the other. The (S) form is metabolized by CYP2C9 and the R-isomer metabolised by CYP1A2, CYP2C19 and CYP3A4.[5] Drugs which interfere with CYP2C9 have a more clinically significant effect on anticoagulation. Examples of inducers include rifampicin and barbiturates while metronidazole is a potent enzyme inhibitor.[2,3]
- Displacement from protein binding sites: The clinical significance of reductions in plasma protein binding by interacting drugs has been debated. Protein-bound warfarin is in equilibrium with free warfarin such that around 99% is bound; displacement of warfarin from serum proteins will result in an increased amount of free drug, making it available to move to the intracellular sites of action and to be excreted. The effect is usually described as transitory and said only rarely to require warfarin dosage adjustment because the increased free drug is metabolised or excreted and a new equilibrium established.[5,6]

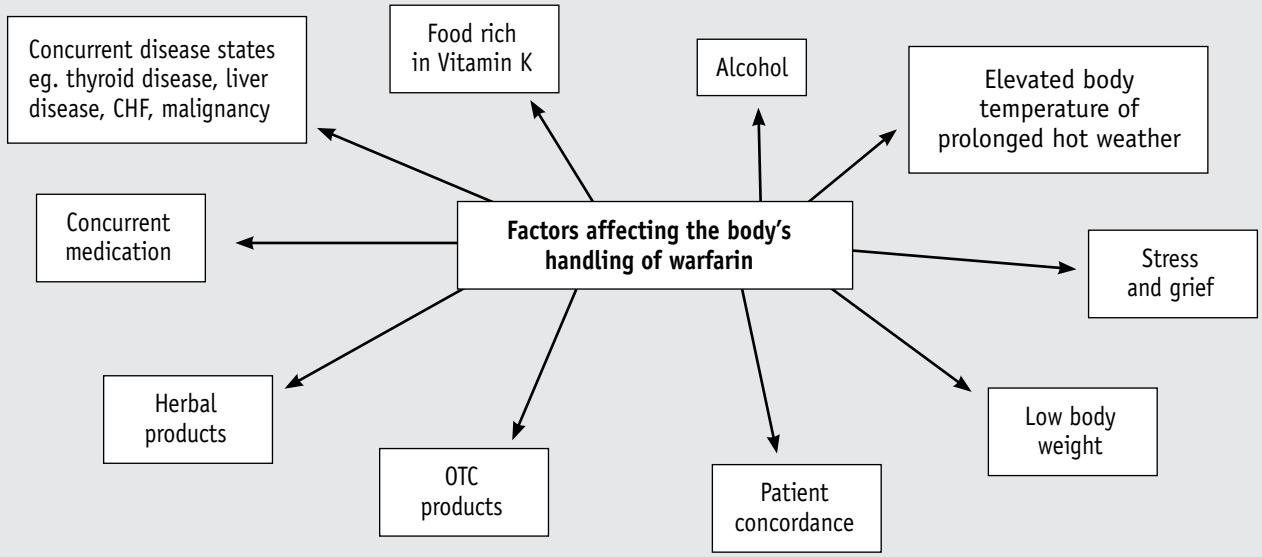
b) Pharmacodynamic interactions:
Some drugs affect platelet function by reducing platelet aggregation. Thus, even though these drugs do not affect the INR, they may be associated with an increased risk of bleeding. Examples include aspirin, dipyridamole, clopidogrel and ticlopidine.[2,3]

Warfarin and alternative therapies

Several alternative therapies may have the potential to interact with warfarin. However, due to a lack of available information, the clinical significance of potential interactions is often unknown since most information is related to *in vitro* data, case reports and theoretical interactions. Overall, patients on warfarin should be advised not to self-treat with such therapies. Often, patients do not mention herbal medications to their health care professional believing that these are safe and will not interact with conventional

Figure 1

Summary of some factors that may affect the body's handling of warfarin



medication.[7,8] One UK study found that as many as 92% of patients who were taking herbal medications with warfarin did not inform a health care professional.[7]

Herbal medications may interact with warfarin as follows: [1,9-12]

a) They may contain substances that have coumarin, salicylate or antiplatelet properties. Though there have been no documented case reports, there is a theoretical risk for potentiation of warfarin activity (e.g., anise, chamomile, red clover)
b) They may interfere with haemostasis and platelet aggregation (e.g., feverfew, garlic, ginger)
c) They may be structurally similar to vitamin K or contain large amounts of vitamin K and consequently have a procoagulant effect (e.g., Coenzyme Q_{10}, Green tea)
d) They may interfere with metabolism of warfarin through inhibition or induction of cytochrome system (e.g., Ginseng and St John's wort both inhibit the cytochrome P450 system)

Dietary supplementation may affect warfarin levels as follows:[10,13,14]

a) Minerals are suspected to bind to warfarin and therefore inhibit its absorption. Administration of warfarin should be separated from intake of these minerals by a period of 2 hours.
b) With the exception of vitamin K, vitamins are unlikely to interact unless taken at doses larger than the recommended daily dose.
c) Vitamin K directly antagonises the effects of warfarin. Therefore patients should be advised to take a vitamin K free preparation or be consistent in the use of multivitamins containing vitamin K.

Table 1 summarises some practice points to aid in the safe management of patients on oral anticoagulation who are also on alternative therapies. Producing an exhaustive reference list of interactions with warfarin is beyond the scope of this review article. The reader is provided with some recommended references at the end.

Warfarin and food

Foods may affect warfarin levels particularly if they contain a high vitamin K content.[15] Table 2 provides a list of such foods. It is important to keep in mind that enteral feeds may contain a large amount of vitamin K. Patients on weight reduction diets tend to have diets based on leafy vegetables which may contain large amounts of vitamin K. In such cases, patients should be advised to keep constant intakes of these foods.[14,15] Alcohol may also affect warfarin levels.[1] Chronic alcoholics may experience a diminished effect from warfarin due to stimulation of hepatic metabolism by alcohol. In the case of 'binge' drinking, there may be an increase in effect of warfarin due to the inability of the liver to metabolise and synthesise clotting factors. Alcohol is considered safe in people with normal liver function provided there is an intake no greater than 2 units daily.[1]

Other factors affecting warfarin metabolism

The following is a summary of possible factors affecting warfarin metabolism:

a) Thyroid disease: Hypothyroidism results in a reduced metabolic rate with clotting factors remaining in the circulation for longer and result in higher requirements for warfarin. When thyroid replacement hormones are administered, the metabolic rate will increase as it returns to normal and clotting factors are metabolised more rapidly. The requirements for warfarin thus decrease. Similarly, when doses of thyroxine are increased, warfarin requirements fall. It is therefore necessary to check the INR after 4–7 days, then weekly until this is stable. The reverse applies if doses of thyroxine are reduced. Hyperthyroidism results in an accelerated metabolic rate with clotting factors being cleared at

Table 1

Ensuring safe use of alternative medications

1.1 Herbal medications also have the potential to interact with warfarin
1.2 Always assume an interaction occurs unless there is evidence to the contrary
1.3 When there is a potential for interaction:
  1.3.1 Patient should be advised to stop the drug before starting warfarin
  1.3.2 If patients insist on taking these medicines, more frequent INR monitoring and closer observation for signs and symptoms of bleeding is recommended
  1.3.3 If a patient self-administers a remedy without advice, it is prudent to ask the patient to stop and recheck INR within 4-7 days and then at regular intervals until stable
1.4 When a documented report of interaction exists, consider the combination as contraindicated due to a potential risk of thrombotic complications
1.5 Ask patients about the use of alternative therapies since they often will not inform you
1.6 Information is often obtained by patients through alternative sources as opposed to health care professionals
1.7 Patients are less likely to report adverse events from herbal interactions
1.8 Herbal products may have several common and scientific names

Table 2

Foods that may affect warfarin levels

Asparagus	Endive (chicory)	Scallion
Avocado	Green beans	Soya bean products
Beef liver	Green tea	Spinach
Broccoli	Kale	Swiss chard
Brussel sprouts	Lettuce (including red)	Tonic water (quinine)
Cabbage (green)	Liver	Turnip greens
Collards (white cabbage)	Mint	Water cress
Coriander	Parsley	

a faster rate. Therefore lower doses of warfarin are required. If antithyroid drugs are administered (eg propylthiouracil or carbimazole), the metabolic rate will slow down and therefore the requirements for warfarin will increase since clotting factors will remain in the blood stream for a longer time.[1,3,13,16]

b) Elevated body temperature (pyrexia or hyperthermia): This results in an accelerated metabolic rate with clotting factors being cleared at a faster rate. Therefore lower doses of warfarin are required.[1,13]

c) Liver disease: This may result in various effects on coagulation, including vitamin K deficiency due to intra- or extra-hepatic cholestasis, reduced synthesis of coagulation factors due to severe hepatocellular damage and functional abnormalities of platelets and fibrinogen found in patients with liver failure. Consequently, the effects on INR are unpredictable and closer INR monitoring is required.[1,13]

d) Stress and grief: These have an unpredictable response. Patients may require closer monitoring in such situations.[1,13]

e) Patient concordance: Possible lack of patient understanding of the risks associated with anticoagulation therapy may result in patient nonconcordance resulting in a variable and unpredictable response.[1,13]

f) Low body weight: Increased sensitivity to warfarin may require reduced dosing.[13]

g) Malignancy: Treatment with cytotoxic agents and metastases to the liver may lead to an increased sensitivity to warfarin.[13]

h) Congestive heart failure: Hepatic congestion due to heart failure may lead to an increased sensitivity to warfarin.[1,13]

Other risk factors that may result in a variable anticoagulation response are: [17-19]

- Multiple warfarin dosage changes (>4 changes within 6 months)*
- Inappropriate warfarin dosage change
- Addition of a new drug potential for interaction (short course antibiotics have been most often implicated)*
- Administration of multiple medications (>4)
- Risk factors for gastrointestinal (GI) tract bleeding include a past history of gastrointestinal bleeding, concomitant use of conventional NSAIDs
- Comorbid conditions associated with higher risk for intracerebral bleeding – including uncontrolled hypertension (persistently > 160/90), cerebrovascular disease, head trauma, concomitant use of conventional NSAIDs
- Malnutrition and malabsorption
- Other decompensating systemic illness (especially infection, disseminated intravascular coagulation).

Evidence is conflicting with respect to patient age with some studies indicating an increased risk and others finding no association between age and oral anticoagulants. The risk-benefit should however be assessed in patients aged over 75.[18] Patients on high intensity anticoagulation appear to have a higher risk of being out-of-control since a higher target INR is usually aimed for.[17,18]

Various studies involving retrospective analysis of patient data have concluded that mortality is lowest when the INR is within

* Most common risk factors implicated

the range of 2.2.-2.3. An INR >6.0 indicates a risk of major haemorrhage in the next 14 days despite no current signs of bleeding.[20]

Adverse effects

The main adverse effects of warfarin are: [1,16,21]

- Increased risk of bleeding which is not necessarily accompanied by a high INR and which is related to the inherent property of warfarin as an anticoagulant. Patients need to be informed about this risk and what action to take in case of bleeding.
- Skin necrosis occurs early in treatment especially in patients who have protein C or S deficiency. The latter are natural anticoagulants also depending on vitamin K for synthesis. Initial treatment with warfarin therefore results in a reduced concentration of the body's own anticoagulants. In such cases, warfarin should be stopped and heparin started.
- 'Purple' toe syndrome is used to describe an acute digital cyanosis secondary to microembolism from a proximal atheromatous source and is common in patients with atherosclerotic disease such as diabetes mellitus, hypertension and peripheral vascular disease. Following such an episode, warfarin should be contraindicated.

Other rare adverse effects include: [1,16,21]

- alopecia
- urticaria, dermatitis
- nausea, diarrhoea and abdominal cramps
- anorexia
- unexplained drop in haematocrit
- jaundice, hepatic dysfunction and pancreatitis.

Contraindications

Contraindications (listed below) depend on individual circumstances and are seldom absolute. It is recommended that an individual's risk/benefit assessment is performed prior to initiating warfarin, and then annually.[1,16,19,21,22]

The following may be considered as **absolute** contraindications:[16,19,22]

- Pregnancy. Due to the teratogenic effects of warfarin, patients receiving warfarin should be warned about the risks prior to conception. Patients who conceive while on warfarin should be advised to seek immediate expert help.
- Bleeding predisposition such as haemophilia
- Thrombocytopenia (<50 x 10^3/µl)
- Uncontrolled hypertension (>160/90). However, this may be considered as reversible if hypertension is adequately treated
- Noncompliance to medication or monitoring.

The following may be considered as **relative** contraindications:[19,22]

- Significant alcohol use (more than 28 units per week for men; more than 21 units for women)
- Conventional NSAID use leading to a greater risk of gastrointestinal bleeding - this may be considered as reversible if replaced with alternative therapy that will allow the patient to take anticoagulants
- Trauma related activities.

This review summarises the numerous factors that may affect the body's handling of warfarin. As the use of warfarin increases and patients' regimens become more complex, maintaining patients' blood levels within the therapeutic range becomes more challenging, with bleeding the major feared adverse effect to prevent. The advent of near patient testing with the availability of immediate INR results, may be the solution to making treatment with warfarin safer in the future.

Annex 1

Useful sources of information

Source	Short Description
Stockley Drug Interactions – A Pharmaceutical Press Publication, 2005	General information related to anticoagulant interactions
Herbal Medications – A Pharmaceutical Press Publication, 2005	Individual drug monographs discuss current evidence. Particularly useful are Appendices 6 and 17 that refer specifically to oral anticoagulants
www.bnf.org	Latest version of British National Formulary – suitable source for warfarin-drug interactions
www.mca.gov.uk	Site for the Medicines and Health Care Regulatory Authority, UK – a useful source of any newly reported interactions between alternative therapies and warfarin
www.fda.gov/medwatch	FDA,USA, safety information and adverse event reporting programme
www.drugs.com	Physician's Desk Reference Information requiring a free first time registration. Exhaustive information on warfarin including interactions and endogenous factors influencing metabolism of the drug
British Society of Haematology www.bcshguidelines.com	Guidelines on Oral Anticoagulation: third edition, 1998
Scottish Intercollegiate Guideline Network www.sign.ac.uk	Antithrombotic Therapy (No.36), March 1999

References

1. Warfarin in practice: A pharmacists' guide to oral anticoagulants in primary care. NES Education for Scotland (Pharmacy). 2004
2. Clinically significant warfarin and drug interactions. University of Washington Medical Centre Anticoagulation Clinics. July 2002.
3. Adams P. Drug Interactions that matter: Warfarin. Pharm J 1998; 261:704-8.
4. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J et al. Oral anticoagulants: mechanism of action, clinical effectiveness and optimal therapeutic range. Chest 2001; 119:8-21.
5. Horn JR, Hansten PD. Enhanced warfarin response and antibiotics. Pharmacy Times June 2004. www.hanstenandhorn.com. Cited: 30th August 2005.
6. Stockley IH (Ed). Drug Interactions. London: Pharmaceutical Press. Electronic Version (6th Edition [2005]).
7. Ramsay NA, Kenny MW, Davies G, Patel JP. Complimentary and alternative medicine use among patients starting warfarin. Br J Haematol 2005;130:777-80.
8. Wong RSM, Cheng G, Chan TYK. Use of herbal medicines by patients receiving warfarin. Drug Safety 2003; 26(8):585-88.
9. Heck AM, Dewitt BA, Lukes AL. Potential interactions between alternative therapies and warfarin. Am J Health-Sys Pharm 2000;57 (13):1221-27.
10. Stenton SB, Bungard TJ, Ackman ML. Interactions between warfarin and herbal products, minerals and vitamins: A Pharmacist's Guide CJHP 2001;54(3): 186-92.
11. Barnes J, Anderson LA, Philipson JD. Herbal Therapeutics (10) Herbal Interactions. Pharm J 2003;270:118–21.
12. Potential warfarin interactions with dietary supplements. University of Washington Medical Centre Anticoagulation Clinics. July 2002.
13. Physician's Desk Reference Information. Warfarin Sodium. www.drugs.com. Cited 8th April 2006.
14. Mason P. Food-Drug Interactions: Nutritional supplements and drugs (2). Pharm J 2002;269:609-11.
15. Mason P. Drug-Food Interactions: Food and Medicines (1). Pharm J 2002;269: 571-73.
16. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. www.bnf.org. Cited 8th April 2006.
17. Brigden ML, Kay C, Le A, Graydon C, McLeod B. Audit of the frequency and clinical response to excessive oral anticoagulation in an out-patient population. Am J Haematol 1998;59:22-7.
18. Levine MN, Raskob G, Landefeld S, Hirsh J. Haemorrhagic Complications of Anticoagulant Treatment. Chest 1995;108 (Suppl 4):276S–90S.
19. Man-Son-Hing M, Laupacis A. Anticoagulant-related Bleeding in Older Persons with Atrial Fibrillation. Arch Int Med 2003;163:1580-6.
20. Oden A, Fahlen M. Oral anticoagulation and risk of death: a medical record linkage study. BMJ 2002;325:1073-5.
21. Wittkowsky Ann K. Thrombosis. In: Young LY, KodaKimble MA. Applied Therapeutics: The Clinical use of drugs. 6th edition. Vancouver. Applied Therapeutics. 1995.
22. Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. Lancet 1998;352: 1167–71.

Practice Points

Aiding safe management of patients on warfarin

- Almost any drug may interact with warfarin.
- Where possible, an interacting drug should be changed for a therapeutically equivalent non-interacting drug.
- When in doubt, check with a suitable source of information
- Patients who are on multiple drug therapy are more prone to an unpredictable response.
- Monitoring is more important during introduction, discontinuation and dosage adjustments of potentially interacting drugs.
- If the drug change lasts < 5 days, either no change in dose, a minor dose reduction or omission of one complete dose of warfarin may be recommended.
- If the drug change lasts > 5 days, it is advisable to check INR one week after the start of the new drug and adjust the warfarin dose on basis of result.
- Where no information about drug interaction is available, one should repeat INR within 4-7 days after starting or stopping treatment.

Erratum

Vella V. Drug-induced peptic ulcer disease. Journal of the Malta College of Pharmacy Practice 2005;10**:**16. The fifth sentence in the second paragraph under the sub-heading 'Bisphosphonates' should have read: Patients should be also be reminded to stand or sit upright for at least 30 minutes after taking the tablet.

MCPP activities during the past year

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The 10th anniversary year has been a very busy one for the College. A range of activities were organised to enhance professional development and practice.

Master Class in Antibiotics and Chemotherapy was the theme of the Autumn PDP. The sessions, delivered by Dr Paul Cuscheri, who is a senior consultant in bacteriology at SLH and a senior lecturer at the University of Malta, addressed, in depth, various aspects of antibiotic therapy.

The Autumn PDP also included an update on the influenza pandemic, delivered by Dr Tanya Melillo, Chairperson of the National Influenza Pandemic Standing Committee and a session entitled 'A psychodynamic approach to counselling' delivered by Juliet Higdon, a Communications Consultant, Trainer and Life Coach.

Regulation of Medicines and Pharmaceutical Activities was the focus of the winter CPD. The Medicines Authority accepted our invitation to provide us with an intensive update in this area. These sessions covered a number of topics including regulations pertaining to pharmacies, pharmaceutical legislation, licensing of medicines, pharmaceutical activities, advertising of human medicinal products as well as adverse drug reactions and pharmacovigilance. These sessions were very well received by participants and were followed by an animated, in depth discussion.

Clinicopathological correlates in dementia was the title of a seminar organized by the Life Science Seminars Organising Committee of Faculty of Medicine and Surgery, University of Malta in collaboration with the Malta College of Pharmacy Practice. The seminar was addressed by Dr John Henry Xuereb, from St Catharine's College Cambridge, UK. This seminar served to stimulate discussion regarding the diagnosis and care of different types of patients suffering from different types of dementias. The associations between specific clinical features and pathophysiological characteristics of these diseases, were described. The discussion was supported with video clips of clinical cases.

Future perspectives of biopharmaceutical research in the EU was the title of an evening seminar organised by the Malta College of Pharmacy Practice in collaboration with Malta Enterprise and with the support of the Medicines Authority. The seminar was addressed by Dr Fergal Donnelly from the Biotechnology and Applied Genomics Unit, Directorate General Research and Technology Development of the European Commission. The seminar addressed issues related to clinical trials, SMEs, pharmaceutical industry R&D, educating professionals for future needs, competitiveness and patient safety.

The Association of Surgeons of Malta invited the Malta College of Pharmacy Practice to endorse, review and accredit their eCME programme. Members of the College can now receive credits for completing on line courses on presentation of a certificate.

Prescription format, content and procedure. Meetings were held with the Medicines Authority and the Associations of Private Family Doctors related to the format, content and presentation of prescriptions as well as to the prescribing procedure. The need to raise this issue was felt after problems related to this area were highlighted by our members.

We are very pleased to note that the Medicines Authority have taken up the matter and will, after the necessary consultation with all stakeholders concerned, be issuing a legal notice under Article 82 of the Medicines Act to stipulate the requirements for a prescription.

The Malta College of Pharmacy Practice 10th Anniversary Dinner was held at the Corinthia Marina Hotel, St Georges Bay, St Julians. It was a delightful evening and a resounding success with the participation of long standing members and friends.

With Thanks

The Malta College of Pharmacy Practice would like to thank all those who have offered their support over the years including individual members, institutions and pharmaceutical sponsors. This year we would like to express our gratitude in particular to the following:

- Mr John Martin Borg and Ms Maria Rossella Dalmas, both of whom are pharmacists and well known artists, for having donated paintings to the College.
- An individual member, who has presented us with a cash donation, and who would like to remain anonymous

The winner of the painting donated by Mr John Martin Borg was Ms Christine Caruana Montaldo. The painting was drawn during the 10th Anniversary Dinner.

Association of Surgeons of Malta: eCME programme

Mr Adrian Agius MD, FRCS (ED) MMed Sc (Bham)

Vice-President, Association of Surgeons and coordinator of the e-learning programme

The Association of Surgeons of Malta has recently launched a new programme of Continuing Medical Education for the medical profession. Co-financed by the European Social Fund and Malta Government the programme consists of a series of modules each dealing with a number of conditions that are often encountered in practice.

The electronic continuing medical education programme of the Association of Surgeons of Malta is endorsed by The Malta College of Pharmacy Practice and will hence be accredited on presentation of certificate indicating successful completion of module.

The first module in this series deals with Vertigo, a common clinical condition that presents to practicing health care professionals from whatever specialty. Two other modules, one on Acute Abdominal Pain and one on Pre-Operative assessment of patients with respiratory problems will be launched shortly.

The modules are aimed at both established medical practitioners practicing in any specialty including family practice as well as doctors in training, clinical year medical students and pharmacists.

The interactive internet-based learning modules enable individuals to home in onto the important practical points that they need to assimilate into their practice. An online course can be completed at a time convenient for the participant and one can progress at one's own pace. Another feature is online discussion with the training faculty. Certification follows successful completion of the module.

The eCME may be accessed through The Synapse www.thesynapse.net