Prescribing, dispensing and patient safety
Editorial 3

An update on the management of hypertension
Marise Gauci 6

A focus on the newer antibiotics targeting Gram-positive bacteria
Antonella P. Tonna, Ivan Tonna, Paul Cuschieri 11

Pharmacogenetics: the path to personalized prescribing
Anthony G. Fenech 16

Benzodiazepines: benefits versus risks
Lorna Marie West 24

Personal experiences of health and illness on the web:
A resource for patients, carers and health professionals
Kath Ryan, Andrew Herxheimer 27

Health perceptions and adherence to diet
Josianne Scerri, Eamonn Ferguson, Christian A. Scerri 33

Gastro-Oesophageal Reflux Disease – GORD
Valérie Vella 38

Medicines: mere generic facts
Vanessa Bugéja 42

Legal Notice 292 of 2006 45
**Wyeth** is one of the world’s leading pharmaceutical and healthcare products companies. Wyeth is research driven, with a major focus on developing innovative new medicines that really make a difference to people’s lives and address significant areas of unmet medical need.

We at Vivian Corporation are extremely proud to be celebrating 50 years of partnership with such an outstanding company, whereby together we will continue to strive to improve the quality of lives of the residents of Malta and Gozo.

...we truly believe in long term relationships!

---

**Wyeth**

50 YEARS of Successful Collaboration

---

A **Prix Galien** award is the most prestigious in the industry. It recognises drug innovation and health benefit. Since 2000, Wyeth have been awarded two, with a commendation for a third.
Prescribing, dispensing and patient safety

Maria Cordina  BPharm(Hons), PhD(QUB)

Editor
Email: president@mcppnet.org

On the 1st December 2006 legal notice 292, Medicines Act (CAP 458) entitled Prescription and Dispensing Rules 2006, came into force. This legal notice seeks to lay down in a very clear manner the legal framework for prescribing and dispensing. It appears to have been welcome by pharmaceutical and medical professional associations as well as by the respective regulating bodies. However, the uptake by practitioners appears to have been slow. It is indeed true that a change in practice tends to take time, yet in this case the stakes are high as the impact is on patient safety.

The collaboration of all stakeholders is necessary for this framework to be effective. Apart from the obvious i.e. pharmacists, the legally recognised dispensers and medical doctors, dentists and veterinary surgeons, the legally recognised prescribers, patients also need to be involved in the process as ultimately they are the ones who experience the effects of the health care system or lack of it.

We also need to take a professional approach and do away with the blame culture. All too often one group of professionals is very ready to blame the other group or even worse, the blame is put on the patient. This is not about blaming either profession, individual professionals or patients but it is about adopting a professional practice that safeguards the health and safety of the patient. Most problems are caused by faulty systems, processes and conditions which lead practitioners to make mistakes or fail to prevent them, subsequently resulting in patient morbidity and possibly mortality. Health care systems are at times criticised...
as being fragmented or even worse for being 'non-systems'. Globally, the current trend is to design healthcare systems to ensure patient safety.2,4

The Legal Notice clearly describes the form and content of the prescription in line with the process of rational prescribing and rational treatment. Rational treatment is a multi-component logical process. First the patient's problem needs to be identified, therapeutic objectives specified, the most appropriate treatment of proven efficacy and safety chosen from a variety of alternatives. The start of treatment is heralded by writing a clear, legible and accurate prescription. This is followed by providing information and instructions to the patient in a manner which he/she can easily comprehend. The patient needs to be monitored to determine if the therapeutic objectives have been achieved. If successful, the treatment can be stopped, if not the above process needs to be repeated.1 In the case of chronic diseases, patients need to be monitored on a regular basis to ensure that they are well controlled.

A prescription is hence an official form of communication between prescriber and pharmacist and should be thus respected. It indicates to the pharmacist that the prescriber has at least engaged in the first part of the above rational therapy process and is assuming responsibility for the therapy prescribed. In the absence of a prescription this cannot be determined.

It is the prescriber's legal obligation to write legibly. Failure to do so could lead to errors resulting in drug misadventure and have a negative impact on the patient. This has been emphasised by the UK Court of Appeal ruling in a case where a doctor wrote a prescription (in a manner which was insufficiently legible) for Amoxicil® which the pharmacist misread and dispensed Daonil®. This resulted in the patient developing permanent brain damage as a result of taking the dispensed drug. The ruling by the UK Court of Appeal implied that doctors are under a legal duty to write clearly, that is with sufficient legibility not to allow for mistakes by others. When illegible, handwriting results in a breach of that duty, causing personal injury. When this is the case the courts will be prepared to punish the careless by awarding sufficient damages. Liability does not end when the prescription leaves the doctor's consulting room. Liability may also be a cause of the negligence of others.4 It is also opportune to note that in the above case, the pharmacist could not have exonerated had the evidence i.e. the prescription, not been produced. It was with this and similar scenarios in mind that the Malta College of Pharmacy Practice emphasised the need for the LN to state that the prescription should be retained by the pharmacist; a recommendation that unfortunately, was not taken up. However, the LN does not state who should retain the prescription and in so doing does not bar the pharmacist from keeping it.

Legibility is not only paramount when writing drug related information but is also essential when writing the prescriber's information relating to name, contact details and the relevant council's registration number. Very often the pharmacist is required to contact the prescriber to discuss therapeutic issues in the best interest of the patient, hence contact details are an absolute necessity. While it may be obvious that the prescriber's name and relevant council number is clearly written, this is very often not the case with the prescription including only an illegible signature. In practical terms this implies that the person responsible for issuing the prescription cannot be identified, unless the relevant council registration number is included (e.g. Medical Council Registration number xxxx). It cannot even be determined if the 'prescription' has originated from an authorised prescriber. This issue assumes even greater consequence when the drug is prescribed for an unlicensed indication, a practice which is on the increase. It is indeed the prescriber's prerogative to prescribe a licensed drug for an unlicensed indication i.e. in breach of the terms of its product licence. In this case there is no doubt that the prescriber (the person who signs the prescription) is assuming all the legal responsibility and placing his/her self in a position of increased vulnerability as he/she may be called upon to justify his/her actions in the event of an adverse event (the manufacturer is only likely to be found liable if harm results from a defect in the product). Pharmacists dispensing a prescription whose prescriber cannot be identified are exposing themselves unnecessarily. Prescribing a drug for an unlicensed indication also presents an additional problem for the pharmacist in terms of patient counselling. This situation necessitates optimal inter-professional communication between prescriber and pharmacist in the best interest of patient care.

The Legal Notice gives further details as to what should be included in a prescription such as patient name, which is essential when the pharmacist is presented with multiple prescriptions and age which is especially important in dosing for children. The duration of treatment is very often omitted. This is of particular importance in terms of expected treatment outcome. If the expected result is not achieved within the stipulated period, the therapy should be reviewed. This needs to be explained to the patient by the pharmacist as the situation may be one of failure to respond to prescribed therapy and the solution may not be to take more of the same as is usually the expectation of the patient. In the case where the prescriber considers that a repeat is required this is provided for in the LN.

The duration of validity of a prescription is specified to be 6 months unless it is a repeat. Repeats are usually issued for patients with chronic conditions such as hypertension and other cardiovascular disease, asthma, diabetes etc. In terms of therapeutic management, it is also essential that these prescriptions are not left 'open'. Patients with chronic disease need to be reviewed on a regular basis, to determine if i) they are responding well to therapy, ii) they are controlled, iii) the prescribed therapy has led to undesirable and unacceptable effects, iv) the original treatment prescribed is still optimal, v) the prescribed treatment is still within currently recommended therapeutic approach and also vi) the condition can be controlled by taking less medication.
In the light of the global public health concern regarding resistance to antibiotics, the validity for such a prescription is only 10 days from date of issue.

It is also important to highlight that verbal instructions over the phone are discouraged and only accepted in a case of emergency and the prescriber should provide the pharmacist with a prescription within 48 hours of the verbal instruction.

Section 4 (2) of the LN clearly states that ‘It shall not be lawful for any pharmacist to dispense any product to which these regulations apply except on a prescription from persons duly authorised…’ Pharmacists argue that in the current situation this is not practical. This may very well be the case but, it must be emphasised that at times, due to practicality they may not be acting in the best interest of the patient as

i) they may be contributing to drug misadventure leading to drug related morbidity and possibly mortality

ii) they may be perpetuating or introducing errors

iii) they may simply be failing to intervene in order to prevent mistakes

iv) they are placing themselves in a position of increased vulnerability.

This cumbersome situation may be addressed in a number of ways. A first step could be reclassification of a number of prescription medicines to non-prescription. This is one of the main recommendations of the G10 Medicines Report which explains that within Europe there already exists a regulatory structure which sets out safety criteria for awarding non-prescription status to medicines. It recommends that ‘For medicines whose indications are currently under prescription but which are regarded potentially suitable for self-medication, a regulatory switch mechanism should be in place encompassing appropriate safety measures.’ The possible advantages cited include a positive impact on public health costs and an ease on the burden of health care professionals.

Pharmacists have a central role in contributing to and ensuring the rational use of medicines. Over the past 40 years there has been a shift from that of a dispenser to the current paradigm of drug therapy manager. Globally it is estimated that for those who receive medicines, more than half of all prescriptions are incorrect and more than half the people involved fail to take them correctly. In addition there is the growing concern regarding the increase of antimicrobial resistance. Pharmacy practice is now patient-centred and includes the functions of counselling, providing drug information and monitoring drug therapy. Within the philosophy of pharmaceutical care pharmacists are involved in all stages of rational drug therapy and assume the responsibility, together with other health care professionals, for the outcomes of drug therapy. The time is opportune to work towards an appropriate structure to be set up in order for pharmacists locally to be able to participate in the patients’ drug management in collaboration with the prescriber and other health care professionals. Programmes exist which enable the pharmacist to detect and manage drug related problems, thereby increasing patient safety. In this age of evidence-based practice, it is important to highlight that evidence exists which illustrates that pharmacists in Malta are competent to deliver Pharmaceutical Care and contribute the patients’ positive health related outcomes. The infrastructure should be set up in practice and should be protected by a legal framework.

As health care professionals we are committed to ensure the health and safety of our patients. During the last Malta Medical School Conference Professor Sir Liam Donaldson, Chair, World Alliance on Patient Safety, set us the challenge of making Malta the safest place in terms of patient safety. We can start by taking small steps and making the effort of respecting the legal framework which promotes rational therapy and patient safety. It is indeed true that we cannot possibly hope to eliminate all errors or drug-related problems but we can most definitely seek to actively practice in a manner which at least enables us to eliminate the avoidable ones. Let us make a concerted effort and work together to achieve this goal.

(A copy of LN292 of 2006 has been included at the back of this journal)

References

1. To Err is human: Building a safer health care system. Linda T. Kohn, Janet M. Corrigan, and Molla S. Donaldson, Editors; Committee on Quality of Health Care in America, Institute of Medicine 2000

Issue 13  Summer 2007

Journal of the Malta College of Pharmacy Practice
An update on the management of hypertension

Marise Gauci B Pharm (Hons), MSc

Clinical Pharmacist, Zammit Clapp Hospital, St Julians, Malta.
Email: marise.gauci@um.edu.mt

Key words: hypertension, cardiovascular risk, thiazides, ACE inhibitors, calcium channel blockers, beta-blockers

This article provides an update on the management of hypertension mostly based on the recent clinical guidelines issued by the National Institute of Clinical Excellence (NICE). Key points being highlighted are the importance of assessment of the cardiovascular disease (CVD) risk and the fact that beta-blockers (BBs) are no longer considered as appropriate first-line agents (in the absence of other indications for beta-blockade). The importance of fully involving patients in treatment decisions on an on-going basis is also emphasised.

Introduction

Hypertension is a major modifiable risk factor for cardiovascular disease. Any definition of hypertension is arbitrary. Consensus from published guidelines is that hypertension is defined as a persistently raised blood pressure (BP) of above 140/90mmHg.

Cardiovascular risk

The co-existence of other modifiable risk factors (e.g. elevated cholesterol, smoking, diabetes) and non-modifiable risk factors (e.g. old age, family history of CVD, male gender) has a bearing on the management strategy for the patient. Health professionals should use a validated risk assessment tool, such as that produced by the Joint British Societies (JBS), as an aid for deciding when treatment is necessary. The latest version of the JBS chart is available in the British National Formulary (BNF).

Treating hypertension should not be viewed in isolation and other interventions, such as statins and aspirin, should be considered on the basis of a person’s history of CVD or an assessment of their CVD risk. The NICE appraisal of statins recommends their use (i) for adults with clinical evidence of CVD (i.e. secondary prevention) and, (ii) as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. Aspirin 75mg daily is recommended for all people with established CVD. Thresholds for using low-dose aspirin to prevent cardiovascular events in people without existing CVD are difficult to define. The British Hypertension Society recommends aspirin 75mg daily for primary prevention in patients with hypertension aged >50 years with BP controlled to <150/90mmHg and either target organ damage, diabetes mellitus, or 10-year CVD risk of ≥20%.

Treatment thresholds and targets

Thresholds for treatment of raised BP consider overall CVD risk, in addition to the absolute BP level. Drug therapy should be offered to patients with persistently high BP of 160/100mmHg or more, and patients at raised CVD risk (10-year risk of CVD of 20% or more, or existing CVD or target organ damage) with persistent BP of >140/90mmHg. Lower thresholds are recommended for patients with diabetes (Table 1).

The evidence base on optimal target BP for both systolic BP and diastolic BP remains incomplete. NICE guidance recommends a BP treatment target of 140/90mmHg for non-diabetic patients. Lower BP targets are recommended for those with diabetes (Table 1). Patients who are at the highest baseline risk of CVD have the most to gain from lowering of BP. Although it may not be possible to achieve target in all patients, any lowering of BP is beneficial. The aim is to achieve the
largest reduction possible toward the target, considering tolerability and concordance for each individual patient.\(^\text{10}\)

**Lifestyle interventions**

A healthier lifestyle, by lowering BP and CVD risk, may reduce, delay or remove the need for long-term therapy in some patients.\(^\text{1}\) All guidelines recommend that lifestyle interventions should form an integral part of the management of high BP either alone or in addition to drug therapy. Key interventions and the associated changes in BP that have resulted from adherence in trials are given in Table 2.\(^\text{1,4}\) Lifestyle modifications can be difficult to achieve and patients need regular follow-up and support to maintain changes in the long-term.

**Drug treatment strategy**

A range of effective antihypertensive drugs from different pharmacological classes can be considered for the treatment of hypertension. In June 2006, NICE updated its guidance on the drug treatment of hypertension. Recommendations were made following a systematic review of randomised controlled trial data which found no difference between the classes of drugs with regard to the risk of death or myocardial infarction. However, BBs were considered less effective than comparable drugs in reducing the risk of stroke.\(^\text{11}\) Thiazide diuretics and calcium channel blockers (CCBs) were considered the most likely drugs to confer benefits in cardiovascular outcomes, except possibly in younger patients. BBs are no longer considered by NICE as an appropriate choice for initial treatment of hypertension unless there are compelling reasons to use them (e.g. coronary artery disease).\(^\text{1}\)

Figure 1 depicts an algorithm for the drug treatment of patients with newly diagnosed hypertension.\(^\text{1}\) Low-dose thiazide diuretics or CCBs are considered by NICE as equal first-line choices for patients over 55 years of age. As the recommendations do not distinguish between the two options, prescribers may decide on the basis of the patient’s risk of adverse effects, patient preference and costs. Angiotensin-converting enzyme inhibitors (ACEIs) are recommended for younger patients. Where an ACEI is indicated but not tolerated (e.g. because of cough), an angiotensin-II receptor blocker (AIIRB) is appropriate. BBs are indicated as initial treatment only in particular situations namely in patients with coronary artery disease, women of child-bearing potential, patients with evidence of increased sympathetic drive, or patients with an intolerance or contraindication to ACEIs and AIIRBs. NICE recommendations for patients already receiving BBs are summarised in Panel 1.\(^\text{1}\)

Many patients will require more than one drug to achieve BP control. Where the first-line drug does not adequately control BP, additional drugs should be added in a sequential manner according to the algorithm. The drug combinations recommended are not supported by large clinical outcome studies, but is based on sound pathophysiological grounds.\(^\text{10}\)

Treatment of patients with hypertension and diabetes was not considered in the development of the updated NICE guideline, and although not explicitly stated, the recommendations do not apply to patients

<table>
<thead>
<tr>
<th>Table 1: Thresholds and targets in the NICE hypertension and diabetes guidelines(^\text{1,7,8})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thresholds for initiating treatment (either systolic or diastolic within ranges)</strong></td>
</tr>
<tr>
<td>Patients without diabetes</td>
</tr>
<tr>
<td>Treat if persistent BP=140-159/90mmHg and 10-year CVD risk ≥ 20% or existing CVD or target organ damage</td>
</tr>
<tr>
<td>Treat all patients with persistent BP ≥ 160/100mmHg</td>
</tr>
<tr>
<td>Patients with type 2 diabetes</td>
</tr>
<tr>
<td>Treat if BP=140-159/80-99mmHg and 10-year CVD risk &gt;20% or concomitant microalbuminuria or proteinuria</td>
</tr>
<tr>
<td>Treat all patients with BP ≥ 160/100mmHg</td>
</tr>
<tr>
<td>Patients with type 1 diabetes</td>
</tr>
<tr>
<td>Treat if BP ≥ 135/85mmHg</td>
</tr>
<tr>
<td>Treat if BP ≥ 130/80mmHg and abnormal albumin excretion rate or two or more features of the metabolic syndrome</td>
</tr>
<tr>
<td><strong>Targets for treatment (both systolic and diastolic BP to be achieved)</strong></td>
</tr>
<tr>
<td>Patients without diabetes ≤ 140/90mmHg</td>
</tr>
<tr>
<td>Patients with type 2 diabetes</td>
</tr>
<tr>
<td>&lt; 140/80mmHg if or ≤ 135/75mmHg if microalbuminuria or proteinuria present</td>
</tr>
<tr>
<td>Patients with type 1 diabetes</td>
</tr>
<tr>
<td>&lt; 135/85mmHg or &lt; 130/80mmHg if nephropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Key lifestyle advice for patients and associated BP reductions(^\text{5,9})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic and Diastolic BP reductions in trials</strong></td>
</tr>
<tr>
<td>Adopt a healthy low calorie diet.</td>
</tr>
<tr>
<td>Take aerobic exercise for 30-60 minutes, three to five times each week.</td>
</tr>
<tr>
<td>Limit alcohol consumption to no more than 21 units/week (men) and 14 units/week (women), with intake spread out over the week.</td>
</tr>
<tr>
<td>Reduce dietary sodium intake to less than 2.4g (100mmol) per day. This is equivalent to 6g of salt.</td>
</tr>
<tr>
<td>Avoid excessive consumption of coffee (≥ 5 cups) and other caffeine-rich products that can raise BP.</td>
</tr>
<tr>
<td>Stop smoking. This has benefits on CVD, if not directly on high blood pressure.</td>
</tr>
</tbody>
</table>
Panel 1: NICE recommendations for patients already receiving a regimen that includes a β-blocker

If BP is controlled, consider long-term management at a routine review. There is no absolute need to replace the β-blocker with an alternative agent.

If BP is not controlled, revise treatment according to the treatment algorithm (see Figure 1).

When a β-blocker is withdrawn, step the dose down gradually.

Do not withdraw the β-blocker if there is a compelling indication for being treated with one, such as symptomatic angina or a previous myocardial infarction.

Figure 1: NICE algorithm for the drug treatment of patients with newly diagnosed hypertension

<table>
<thead>
<tr>
<th>&lt;55 years</th>
<th>≥ 55 years or black* (any age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>A† or C or D</td>
</tr>
<tr>
<td>Step 2</td>
<td>A+C or A+D</td>
</tr>
<tr>
<td>Step 3</td>
<td>A+C+D</td>
</tr>
<tr>
<td>Step 4</td>
<td>A+C+D + further diuretic therapy, or α-blocker, or β-blocker</td>
</tr>
</tbody>
</table>

Consider specialist advice

---

*of African or Caribbean descent, and not mixed race, Asian or Chinese
†β-blockers are an alternative to A in patients younger than 55 years if A is not tolerated or is contraindicated (including women of childbearing potential)

A=ACEI e.g. enalapril 5-20mg once dly
lisinopril 10-20mg once dly
perindopril 4-8mg once dly

or AIIRB e.g. candesartan 8-16mg once dly
(eprosartan 600-800mg once dly
losartan 50-100mg once dly
telmisartan 40-80mg once dly
valsartan 80-160mg once dly

C=calcium channel blocker e.g. amlopidine 5-10mg once dly
D=thiazide-type diuretic e.g. bendroflumethiazide 2.5mg once dly
indapamide 1.5mg once dly

β-blocker e.g. atenolol 50mg once dly
α-blocker e.g. doxazosin 4-8mg once dly, terazosin 2-10mg once dly

usual maintenance doses; lower dose may be required in elderly and in renal or liver impairment

with diabetes. In these patients, a thiazide diuretic or an ACEI is an appropriate first-line choice, with a combination of these two drugs being used should BP control not be achieved. An ACEI should be used first-line where there is evidence of nephropathy.

Patient perspective

Decision on treatment goals should be reached in full discussion with patients, since the trial evidence does not support one target BP. The aim should be to achieve as great a reduction in BP toward the target as is acceptable to the patient.

Patients have reservations about taking their antihypertensive medication (e.g. preference for non-drug measures to lower BP, anxiety about potential side effects of treatment, doubt whether treatment continues to be necessary).

NICE guidelines recommend that all patients should have an annual review of care to monitor BP, provide support, and discuss lifestyle, symptoms and medication.

It is estimated that 50–80% of patients with hypertension do not take all of their prescribed medication. Reasons include the asymptomatic nature of hypertension, the need for long-term treatment, complex drug regimens, poor instructions, and disagreement about the need for treatment.

Non-adherence to medication should be considered when evaluating a patient with poor BP control.

Understanding a patient’s reasons for not taking their medication is important for implementing effective strategies to improve the management of their hypertension.

Conclusion

Managing hypertension is a challenge for both health professional and the patient. Updated guidelines should be utilised so as to provide optimal treatment and improve patient outcomes. Full involvement of patients in treatment decisions and regular review are essential for effective management.
The National Institute for Health and Clinical Excellence (NICE) has published new guidelines: Secondary prevention in primary and secondary care for patients following a myocardial infarction. The guidelines include a section highlighting important lifestyle changes which patients who have suffered an acute myocardial infarction should adopt:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommended advice for patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving diet</td>
<td>Advise patients not to take supplements containing beta-carotene.</td>
</tr>
<tr>
<td></td>
<td>Do not advise patients to take antioxidant supplements (vitamin E and/or C) or folic acid to reduce cardiovascular risk.</td>
</tr>
<tr>
<td></td>
<td>Advise patients to consume at least 7 g of omega 3 fatty acids per week from two to four portions of oily fish.</td>
</tr>
<tr>
<td></td>
<td>Consider providing at least 1 g daily of omega-3-acid ethyl esters treatment licensed for secondary prevention post MI for up to 4 years for patients who have had an MI within 3 months and are not achieving 7 g of omega 3 fatty acids per week.</td>
</tr>
<tr>
<td></td>
<td>Do not routinely initiate omega-3-acid ethyl esters supplements for patients who have had an MI more than 3 months earlier.</td>
</tr>
<tr>
<td></td>
<td>Encourage patients to eat a Mediterranean-style diet.</td>
</tr>
<tr>
<td>Delivering dietary advice</td>
<td>Give consistent healthy eating advice that is tailored to the patient's needs and that can be extended to the whole family.</td>
</tr>
<tr>
<td></td>
<td>Offer patients an individual consultation to discuss diet, including their current eating habits, and advice on improving their diet.</td>
</tr>
<tr>
<td>Controlling alcohol consumption</td>
<td>Advise patients to keep weekly alcohol consumption safe limits (no more than 21 units of alcohol per week for men or 14 units per week for women) and to avoid binge drinking.</td>
</tr>
<tr>
<td>Improving physical activity levels</td>
<td>Encourage patients to undertake sufficient regular physical activity to increase exercise capacity.</td>
</tr>
<tr>
<td></td>
<td>They should aim to be physically active for 20-30 minutes a day to the point of slight breathlessness.</td>
</tr>
<tr>
<td></td>
<td>For patients not achieving this, advise them to increase their activity in a step-by-step way, aiming to increase their exercise capacity. They should start at a level that is comfortable, and increase the duration and intensity of activity as they gain fitness.</td>
</tr>
<tr>
<td></td>
<td>Discuss current and past activity levels and preferences with patients.</td>
</tr>
<tr>
<td></td>
<td>The benefit of exercise may be enhanced by tailored advice from a suitably qualified professional.</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Advise smokers to quit and offer assistance from a smoking cessation service.</td>
</tr>
<tr>
<td></td>
<td>Offer smokers who have expressed a desire to quit support, advice and referral to an intensive support service.</td>
</tr>
<tr>
<td></td>
<td>If a patient is unable or unwilling to accept a referral, offer pharmacotherapy.</td>
</tr>
<tr>
<td></td>
<td>Refer to NICE technology appraisal guidance 39 and NICE public health intervention guidance 1.</td>
</tr>
<tr>
<td>Controlling weight</td>
<td>Offer overweight and obese patients advice and support to achieve and maintain a healthy weight.</td>
</tr>
</tbody>
</table>

Proven to save lives in post-MI patients. It's a fact.¹

OMACOR reduces the risk of mortality by 20%¹

Highly purified Omega-3 ethyl ester

OMACOR®

• Hypertension is a major modifiable risk factor for cardiovascular disease.
• The co-existence of other modifiable risk factors has a bearing on the management strategy for the patient (CVD risk assessment).
• Drug therapy should be offered to patients with persistently high BP of 160/100mmHg or more, and patients at raised CVD risk (10-year risk of CVD of 20% or more, or existing CVD or target organ damage) with persistent BP of >140/90mmHg.
• BBs are no longer considered by NICE as an appropriate choice for initial treatment of hypertension unless there are compelling reasons to use them (e.g. coronary artery disease).
• Patients should be involved in treatment decisions on an on-going basis.

References

12. Benson J, Britten N. Keep taking the tablets: balancing the pros and cons when deciding to take blood pressure treatment. BMJ 2003; 326:131–.
A focus on the newer antibiotics targeting Gram-positive bacteria

Antonella P. Tonna1 MRPharmS, BPharm (Hons), MSc
Ivan Tonna2 MD, MRCP (UK), MSc (Infectious Diseases), DLSTM
Paul Cuschieri3 MD, FMCPath, FRCPath (UK), Dip Bact (Manch)

1PhD student/Ad hoc Lecturer, School of Pharmacy
Faculty of Health and Social Care, The Robert Gordon University,
Schoolhill, Aberdeen, Scotland
Email: prs.tonna@rgu.ac.uk

2Specialist Registrar Infectious Diseases, Infectious Diseases Unit
Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Scotland

3Consultant Microbiologist, Microbiology Department
St Luke’s Hospital, G’Mangia, Malta

Key words: antibiotics, Gram-positive, multi-drug resistant, daptomycin, tigecycline, linezolid

The incidence of antimicrobial resistance has continued to rise with a threat to return to the “pre-antibiotic” era. This has included a sharp increase in multi-drug resistant organisms, which may cause life-threatening infections. Efforts have been made to develop new antibiotics with novel modes of action, aimed at acting against these multi-drug resistant strains. This review aims to focus on newly available and investigational antibiotics targeting Gram-positive organisms. It is likely that these antibiotics will be used mainly in a secondary care setting; however primary care health care professionals also need to have an understanding of these antibiotics, since patients may be discharged home on them.

Introduction
Antimicrobial resistance and the threat this brings with it have long been recognised. Inherent antimicrobial resistance existed even before antimicrobials were introduced into medicine; in 1940, Abraham and Chain recognised acquired antimicrobial resistance when, during the development of penicillin, they isolated an enzyme (now termed penicillinase) that destroys penicillin. Due to the international and fast spread of microorganisms in this era of mass travel and global trade, the problem of antimicrobial resistance no longer remains a national one. Rather it is a European and global problem requiring international cooperation and a global strategy to avoid returning to the “pre-antibiotic” era. The inferior quality of poorly formulated or manufactured antimicrobials in the less developed world, where medications are often used after their expiry date, adds to the complexity of the problem. This has been further compounded by factors in secondary care including hospital over-crowding leading to cross-infection, immunosuppression (due to disease or its treatment) and the use of more invasive techniques which provide access for easy entry of bacteria into the patient’s body.

Despite improvements in immunization, infection control policies and medical practice amongst others, the rate of emergence of resistant strains has continued to rise, with a nearly 25% increase in resistance among Gram-positive pathogens in the United States over a ten year period. The most common drug resistant Gram-positive pathogens are staphylococci, enterococci and streptococci with meticillin resistant Staphylococcus aureus (MRSA), vancomycin resistant Staphylococcus aureus (VRSA) and vancomycin resistant Enterococcus species (VRE) offering the greatest challenge to health care and causing potentially life-threatening infections. Multi-drug-resistant Streptococcus pneumoniae has also been reported. Reports indicate that more than 25% of Staphylococcus aureus infections in Europe are caused by MRSA, with most of these isolates being multi-drug resistant. The European Union has voiced its concern about this alarming increase in antibiotic resistance and has launched a surveillance programme, the European Antimicrobial Resistance Surveillance System (EARSS). A recent report summarising trends over the past seven years (1999 to 2006), has indicated that there continues to be a loss of antimicrobial effectiveness which does not seem to have slowed down, with resistance and a reduction in antimicrobial effectiveness reported both in community and in hospital-based care.

The purpose of this review is to describe some of the newer compounds targeting mainly Gram-positive organisms, including multi-drug resistant strains. The review will also briefly describe some compounds in various stages of clinical development.

Daptomycin
Daptomycin is a fermentation product produced by Streptomyces roseosporus. It was originally discovered by Eli Lilly in the 1980s and given the name deptomycin, which was later changed due to potential
Short term:
- Faster symptom relief
- Superior clinical cure

Long term:
- Longer exacerbation-free interval
- Positive influence on outcome

2. Wilson, R et al. CHEST. 2004;125(3):953-964

Abbreviated Prescribing Information. See local prescribing information for full details for Avalox film-coated tablets or infusion solution containing 400 mg moxifloxacin. Indications: Respiratory Tract Infections: Acute exacerbations of chronic bronchitis. Community Acquired Pneumonia. Acute Sinusitis. Soft Tissue Infections. Treatment is indicated for adults (18 yr of age). Dosage: The recommended daily dose is one tablet or infusion solution (400 mg) once daily for all indications. Infusion rate for the infusion solution, 60 minutes. General recommendation for acute exacerbation of chronic bronchitis: 5 days. Community acquired pneumonia: 10 days. Acute sinusitis: 7 days. Soft tissue infections: 7 days. Moxifloxacin can be administered orally or intravenously for the entire treatment duration. Alternatively, therapy may be initiated intravenously after oral tablet administration when allowed by the patient’s condition. Contraindications: Hypersensitivity to moxifloxacin or other ingredients of the infusion solution or other quinolones, children, growing adolescents, pregnancy, and nursing mothers. Precautions: Known or suspected CNS disorders (seizures), severe hepatic impairment, patients with known prolongation of the QT interval, uncorrected hypokalemia and patients receiving class IA or class III antiarrhythmic agents, concurrent use of QT interval prolonging drugs, proarrhythmic conditions. Recommended dose and infusion rate of 60 minutes should not be exceeded as this may increase QT prolongation which may lead to an increased risk for ventricular arrhythmias including Torsades de pointes, QTc prolongation, proarrhythmic events. Cautions: Excessive exposure to UV radiation or sunlight. To some extent, hypersensitivity, allergy, reactions and anaphylactic reactions until death occurring immediately after first administration. Interactions: Antacids, anti-emetics and other preparations containing magnesium, aluminium, sucralfate and other agents containing iron or zinc should be administered at least 4 hours before or 2 hours after ingestion of an oral moxifloxacin coil. Carboxymedications reduces systemic exposure after intravenous drug administration by approx 20% and after oral drug administration by more than 80%. Side effects: 1% < 10%; abdominal pain, headache, injection site reaction. QT prolongation in patients with concurrent hypokalemia, nausea, diarrhea, vomiting, dizziness, abnormally low serum potassium level, some tremors, dizziness, 0.1% <1%; fever, malaise, pain, muscle cramps, tachycardia, hypertension, palpitations, QT prolongation, phlebitis (at infusion site). Dry mouth, nausea and vomiting, flatulence, constipation, oral mucositis, anorexia, stomatitis, gastrointestinal disorders, glossitis. gGT increased, leucopenia, prothrombin decrease, eosinophilia, thrombocytopenia, anemia increase, anemia, myalgia, insomnia, vertigo, nervousness, somnolence, anxiety, tremor, paresthesia, dyspnea, rash pruritus, sweating, vaginal moniliasis, vaginitis. 10% < 0.1%; pelvis pain, face edema, back pain, lab test: abnormal, allergic reaction, leg pain, hypotension, vasodilatation, peripheral edema, edema, tinnitus, disorientation, dysphagia, jaundice, diarrhea (Clostridium difficile), cholecystis, tenesmus, hemorrhoids, ulcer, ulceration, angina, anemia, leukocytosis, eosinophilia, thrombocytopenia, fever, increased BUN. Common in laboratory parameters without regard to drug relationship increased and decreased hematocrit, increased WBC, increased and decreased BUN, increased diastolic BP, increased alkaline phosphatase, increased SGOT/AST, increased SGPT/ALT, increased bilirubin, increased uric acid, increased creatinine, increased BUN. Ability to drive or operate machinery may be impaired. Marketing Authorisation Holder: A Gera 6 Sens, 10 Tràd-à- Massar, Qormi QRMD127. tamsin@alphajera.com
renal impairment where the creatinine should be increased to every 8 hours in
and consequently the dosage interval prolonged post-antibiotic effect of more
not be removed.
the presence of foreign devices that could
and was associated with prolonged use and
species.
first drug with bactericidal activity against
where mixed infections are suspected.
should not be administered as monotherapy
in Gram-negative
aureus.
More recently, it has also been
in vitro
between the two for meticillin-sensitive
surgical site infections secondary to MRSA.
were equivalent in the intention-to-treat
randomised trials of patients with MRSA-
rate of cure and a lower mortality than
linezolid was noted to have a higher
documented hospital-acquired pneumonia,
Gram-positive infections. Its use is mainly
in cases of multi-drug resistant infections
such as MRSA, GISA and VRE. Hence, it
is more likely to be used in the hospital setting.
Currently, the approved indications
for use of linezolid include hospital-acquired pneumonia (especially ventilator-associated pneumonia) and cSSTI.
A number of trials have been carried
out in order to assess the efficacy of
linezolid compared to other well established
treatment regimens, including a randomized
control trial comparing linezolid with
vancomycin in the treatment of cSSTI. The
results showed that the two drugs were
equivalent in the intention-to-treat
analysis. However, linezolid was noted
to be superior where MRSA was isolated
and in those patients with abscesses and
surgical site infections secondary to MRSA.
The authors of this paper suggest that the
better outcome with linezolid could be due
to better penetration of the drug into skin
and subcutaneous tissue.

In an analysis of two double-blind
randomised trials of patients with MRSA-
documented hospital-acquired pneumonia,
linezolid was noted to have a higher
rate of cure and a lower mortality than
vancomycin. There was no difference
between the two for metillin-sensitive
Staphylococcus aureus (MSSA) infections.
As with CSSTI, it is thought that linezolid
penetrates lung tissue better than
vancomycin. As a result of this study and
two others based on tissue penetration of
linezolid, the American Thoracic Society's
guidelines on the treatment of hospital-
the bacterial ribosome which is important
for the initial phase of protein translation. Hence, it has no effect on bacterial
replication or transcription of DNA to RNA.
Linezolid is bacteriostatic. It has
good activity against Gram-positive
bacteria, including MRSA, glycopeptide-
intermediate Staphylococcus aureus (GISA),
VRE and penicillin-resistant Streptococcus
pneumoniae. Moreover, it is also active
against anaerobes, such as Clostridium
perfringens and Peptostreptococcus species.
The drug is available in both oral
and intravenous forms. The oral dose is
600mg bd. Bioavailability following oral
administration is 100% and absorption is
not affected by food. Elimination half
life of the drug is 4.5 to 5.5 hours after a
steady state has been reached.
Although bacteriostatic, linezolid has an
important role in the treatment of serious
Gram-positive infections. Its use is mainly
in cases of multi-drug resistant infections
such as MRSA, GISA and VRE. Hence, it
is more likely to be used in the hospital setting.
Currently, the approved indications
for use of linezolid include hospital-acquired pneumonia (especially ventilator-associated pneumonia) and cSSTI.
A number of trials have been carried
out in order to assess the efficacy of
linezolid compared to other well established
treatment regimens, including a randomized
control trial comparing linezolid with
vancomycin in the treatment of cSSTI. The
results showed that the two drugs were
equivalent in the intention-to-treat
analysis. However, linezolid was noted
to be superior where MRSA was isolated
and in those patients with abscesses and
surgical site infections secondary to MRSA.
The authors of this paper suggest that the
better outcome with linezolid could be due
to better penetration of the drug into skin
and subcutaneous tissue.

In an analysis of two double-blind
randomised trials of patients with MRSA-
documented hospital-acquired pneumonia,
linezolid was noted to have a higher
rate of cure and a lower mortality than
vancomycin. There was no difference
between the two for metillin-sensitive
Staphylococcus aureus (MSSA) infections.
As with CSSTI, it is thought that linezolid
penetrates lung tissue better than
vancomycin. As a result of this study and
two others based on tissue penetration of
linezolid, the American Thoracic Society's
guidelines on the treatment of hospital-

...
acquired pneumonia suggest that patients with documented MRSA pneumonia could be treated with either vancomycin or linezolid, but the latter should be preferred if patients have renal impairment or are at risk of nephrotoxicity.²⁶

There are also case reports of linezolid being used in other disease states, such as infective endocarditis²⁷, central nervous system infections²⁸ and bone/joint infections²⁹, but its use has been hampered by a lack of safety data on long term use.

Adverse events associated with linezolid use include anaemia, neutropaenia, thrombocytopenia, deranged liver function, headaches and gastrointestinal disturbances.²⁰ It is recommended that patients who are on linezolid should have their full blood count checked every week whilst on treatment, especially if the duration of the antibiotic continues beyond the recommended maximum of 28 days.¹³

Linezolid is an inhibitor of monoamine oxidase inhibitors (MAOIs). Hence, it should be avoided in patients on MAOIs unless it is given under close supervision.³¹ There have also been reports of the serotonin syndrome when the antibiotic was administered with serotonin reuptake inhibitors (SSRIs); this can occur early during treatment in young patients but later in older patients.²¹

Although linezolid is a novel antibiotic with a different site of action than any other antibiotic, resistance has been seen in some cases. Most of the cases have been noted in patients who have either indwelling prosthetic devices or have been receiving prolonged courses of the antibiotic.²²

**Tigecycline**

Tigecycline belongs to a class of drugs, closely related to tetracycline, called glycylcyclines. It inhibits protein synthesis by binding to the 30S ribosomal subunit and preventing the addition of transfer RNA molecules required for the elongation phase.²³

Tigecycline is a bacteriostatic drug.²⁴ In this respect, it is similar to linezolid. Its antibacterial spectrum is however much more extensive, with excellent activity not only against Gram-positive organisms but also against Gram-negatives. It is very potent against MRSA, VRE, meticillin-resistant *Staphylococcus epidermidis* and streptococci (including penicillin-resistant strains). Moreover, it is active against many Gram-negatives including *Enterobacteriaceae* and multidrug resistant *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*. On the other hand, it has reduced activity against *Proteus* and *Pseudomonas aeruginosa*.²⁵

Tigecycline is only available as an intravenous preparation because oral bioavailability is poor.²³ The currently recommended dose is a 100mg loading dose followed by 50mg twice daily. The half life in humans ranges between 37 and 67 hours. It is widely distributed in the body with concentrations in skin and lungs reaching three times that of plasma in experimental rats.²⁶ Tigecycline circulates as unchanged drug in serum. It is eliminated through the gut and hence, does not need any dose adjustment in patients with renal failure.²⁷

The current indications for tigecycline are cSSTI and complicated intra-abdominal infections.²⁴ In the case of cSSTI, results from two phase 3 randomised, double-blinded studies were pooled and analysed.²⁸ Patients were treated with either tigecycline monotherapy or vancomycin plus aztreonam for up to 14 days. The results showed that tigecycline was as effective as the comparator arm. On the other hand, in the case of complicated intra-abdominal infections both Gram-positive and Gram-negatives are important in the pathogenesis of this disease. In a pooled analysis from two Phase 3 studies between tigecycline monotherapy versus imipenem-clastatin in 1642 adults with complicated intra-abdominal infections, it was shown that tigecycline was non-inferior to the comparator arm.²⁹

Tigecycline is very well tolerated. The most frequent adverse events reported to date include nausea and vomiting, resulting in discontinuation of treatment in 5% of cases.³⁰ Other relevant events are transient elevations of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase, which are all markers of hepatic function.

There are very few drug interactions of clinical significance, when administering tigecycline. Since it is not metabolised by the liver there is no effect on drugs acting on the cytochrome P450 enzyme system.²³ Although tigecycline may prolong both prothrombin time and activated partial thromboplastin time, there is no evidence to suggest that this may result in a significant change in the INR. However, it is advisable that patients on warfarin should be more closely monitored if they are administered tigecycline concurrently.³¹

Currently, resistance to tigecycline is not a major problem. It is known that tigecycline binds more avidly to ribosomes than tetracycline and hence can overcome the resistance methods employed against the latter. However, resistance can emerge in microorganisms that are able to express the multi-drug efflux pump normally associated with Gram-negatives.³¹

**Other antibiotics under development**

With the emergence of ever more drug resistant microorganisms, the need for developing more active drugs is a real emergency. The antibiotics mentioned above have all been approved for specific clinical indications. There are other investigational drugs which are at different stages of development. Their main target is multi-drug resistant bacteria.

- **Dalbavancin** is a semisynthetic glycopeptide with a similar mode of action to vancomycin. It has potent activity against Gram-positive organisms including MRSA.³² This drug is remarkable for its long half life of 8.5 days and can therefore be used once weekly. In a number of trials involving this drug, it was administered on day 1 and day 8 only for cSSTI.³³,³⁴ This drug could be very useful in the outpatient treatment of cSSTIs. Its long half-life may be a major drawback since if there is a drug related reaction, its effects will last for a number of days and cannot be reversed by simply stopping the drug.

- **Other semisynthetic glycopeptides** used against Gram-positive organisms including MRSA are under investigation. *Telavancin* is rapidly bactericidal and exists as an intravenous preparation to be given once daily. Its current indication is in cSSTI.³⁵ *Oritavancin* is still in a Phase 3 study. Its indications are likely to include cSSTI, catheter-associated infections and endocarditis. Because of a long half life, it is likely that it will be dosed on a daily or alternate day schedule.³²

- **Ceftobiprole** is a novel bactericidal cephalosporin being developed for the treatment of Gram-positive organisms, including MRSA, whilst maintaining the Gram-negative cover of the third generation cephalosporins. At the time of writing, the drug is in a Phase 3 trial and the indications are thought to include cSSTI.³⁶
Iclaprim is a new dihydrofolate reductase inhibitor belonging to the same class of antibiotics as trimethoprim. Its Gram-positive cover is very promising with potent activity against MRSA, VISA and VRSA. It is currently in development as an intravenous agent; however, oral bioavailability is good and there are Phase I trials with an oral preparation which would allow intravenous-to-oral switch.37

Conclusion
As more resistant organisms are being seen in clinical practice, there is an urgent need for more potent antibiotics. There are only a few drugs which belong to a completely novel class; the rest are only a development of old and existing classes. If we do not take good care of the existent antibiotics by responsible prescribing, we will be at risk of losing even these more efficacious antibiotics.

References
2. Emerging and other communicable diseases; antimicrobial resistance. World Health Organization Bill 51.17 Fifty-first World Health Assembly.
Pharmacogenetics:
the path to personalized prescribing

Anthony G. Fenech BPharm(Hons), PhD

Lecturer, Department of Clinical Pharmacology and Therapeutics, University of Malta, Malta
Email: anthony.fenech@um.edu.mt

Key words: pharmacogenetics, pharmacogenomics, personalized prescribing

The fact that different patients may show dissimilar responses to the same drug, has been recognised for several years, and many variables, such as age, gender and body weight have been identified to contribute to this observation. The last half century has seen a rise in research concerning a new variable – genetic variation – which has been recognised to offer a major contribution to this phenomenon. Pharmacogenetics research has today established itself as an important arm of pharmacology, and has key applications in drug development and clinical therapeutics. The advent of high throughput methodologies coupled with new data derived from the human genome sequencing project, has helped to powerfully mobilise the developmental pace of this research work, and to introduce the concept of genome-wide pharmacogenetic studies, or pharmacogenomics. The eventual development of pharmacogenetic tests, able to identify patients who are most likely to adequately respond to specific therapies from those who are not, will be a landmark in the history of therapeutics, and coupled to the development of new drugs for specific pharmacogenetically-stratified patient populations, will provide a markedly enhanced toolkit for the optimization of the benefit-risk ratio in prescribing.

Introduction
Pharmacogenetics and pharmacogenomics are terms which are today soundly entrenched within pharmacological and pharmaceutical literature. The term pharmacogenetics was used for the first time by Friedrich Vogel in 1919, who coined it to describe the influence of genetic factors on the response to drugs. In the following years, the number of peer-reviewed scientific publications dealing with this area, started to show a steady rise, while the last 10 years has suddenly seen an exponential increase. This is a reflection of the research explosion which has recently been occurring in this area. A cursory look at the Medical Subject Heading (MeSH) fields of the National Library of Medicine Pubmed database, which to-date indexes over 11 million articles gives evidence to this (Fig. 1). Rubin and his workgroup recently reported on their use of an automated system, based on an algorithm designed to specifically data-mine biomedical literature databases for pharmacogenetics knowledge in order to extract specific reference lists which are more focused to a specific topic, than manual Boolean operator-linked multiple field search methods can provide.

This article will review the relevance of this research area, and its implications to pharmacological therapeutics.

Pharmacogenetics and pharmacogenomics
The advent of novel research technologies, allowing high throughput screening of large numbers of biomolecules has ushered us into the –omics era of new methodologies such as transcriptomics (the large-scale study of the cell transcriptome), metabolomics (the large-scale study of metabolite profiles), proteomics (the large-scale study of proteins) and in 1995, pharmacogenomics. Unfortunately, throughout the recent past, pharmacogenomics has often been used interchangeably with pharmacogenetics, blurring the large-scale gene-study implications inferred by the former term. The Nuffield Council on Bioethics, UK, defines pharmacogenetics as “the study of the effects of genetic differences between individuals in their response to medicines” and pharmacogenomics as “the examination
Catalyst 50 mg powder for oral solution
Presentation: Diclofenac potassium powder for oral solution in sachets of 50 mg. Indications: Short-term treatment of the following acute conditions: post-traumatic pain, inflammation and swelling, e.g. due to sprains, post-operative pain, inflammation and swelling, e.g. following dental or orthopedic surgery, pain and/or inflammation conditions in gynaecology, e.g. primary dysmenorrhea or adenitis, migraine attacks, painful syndromes of the vertebro-sacral column, non-vascular uveitis, as an adjuvant in severe painful inflammatory infections of the ear, nose or throat. Dosage: Dose to be individually adjusted, lowest effective dose to be given for the shortest duration. Adults: 50 to 100 mg daily in divided doses. For dysmenorrhea and migraine attacks: 1 to 2 sachets per day. Adolescents aged 14 and over: 50 to 100 mg daily in divided doses. Not recommended in children and adolescents below 14 years of age. Contraindications: Active gastric or intestinal ulcer, bleeding or perforation, known hypersensitivity to diclofenac or to any of the excipients, to asprin or other non-steroidal anti-inflammatory drugs (NSAIDs), last trimester of pregnancy, severe hepatic, renal or cardiac failure. Precautions:

-WARNINGS: Avoid use with other systemic NSAIDs including COX-2 inhibitors. Risk of gastrosophageal ulceration, perforation or serious allergic reactions, to be discontinued if these conditions occur. Risk of allergic reactions. May mask signs and symptoms of infection. Caution recommended in patients with symptoms/history of I1 disease, asthma, seasonal allergic rhinitis, chronic pulmonary diseases, elderly or impaired hepatic function (including pruritus), ulcerative colitis or Crohn's disease. Caution when used concomitantly with corticosteroids, anticoagulants, anti-platelet agents or SSRIs. Caution while driving or using machines. Should not be used in the first and second trimester of pregnancy and by breast feeding mothers. Not recommended in use in women attempting to conceive as it may impair female fertility. Combined use with protective agents to be considered in patients with history of ulcer, elderly and those requiring low dose aspirin. Monitoring of liver function and blood counts recommended during prolonged period. Monitoring of renal function recommended in patients with history of hypertension, impaired cardiac or renal function, extracorporeal volume depletion, the elderly, patients treated with diuretics or drugs that impact renal function. Monitoring recommended in patients with decret of haemocys. As Catalyse contains a source of phenylalanine, may be harmful for patients with phenylketonuria. Beware of severe fluid retention and oedema.

-INTERACTIONS: Caution with concurrent use of diuretics and anti-hypertensives (e.g. beta blockers, ACE-inhibitors), metformin, other NSAIDs and corticosteroids, SSRIs. Monitoring recommended for patients receiving anticoagulants, anti-platelet agents as well as blood glucose level if used concomitantly with antileptic. Monitoring of serum lipid and digoxin levels recommended if used concomitantly. Dose of diuretics to be reduced in patients receiving diclofenac. Clinica interactions with concomitant use of cimetidine or allopurinol. Adverse reactions:

-Common undesirable effects are: Headache, dizziness, vertigo, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, constipation, anorexia, transaminases increased, rash. Rare undesirable effects are: Hypersensitivity angioedema and angioedema-like reactions (including hypotension and shock), secondary asthma (including dyspnoea, asthma, gastrointestinal haemorrhage, haematemesis, melena, diarrhoea, haemorrhage, gastrointestinal ulcer with or without bleeding or perforation), hepatitis, jaundice, liver disorder, urticaria, oedema. Very rare undesirable effects are: Trombocytopenia, leukopenia, anemia (including haemolytic anaemia and aplastic anaemia), agranulocytosis, angioneurotic oedema (including face oedema), disorientation, depression, insomnia, nightmares, irritability, psychoactive disorder, paraesthesia, nervous impairment, confusion, anxiety, tremor, asthenia, tremor, dizziness, vertigo, dyspepsia, abdominal pain, constipation, chest pain, cardiac failure, myocardial infarction, hypertension, tachycardia, tachypnoea, cough, cold, fever, flu, headache, influenza, rhinitis, sneezing, urticaria, angioedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedema, urticaria, angioedema, angioneurotic oedematous. References:

of whole genomes or substantial numbers of genes in order, for example, to identify putative targets for medicines or to identify large-scale differences in the patterns of gene expression in response to chemical compounds. The National Centre for Biotechnology Information (NCBI), USA, uses a similar distinction between the terms and defines pharmacogenetics as “the study of inherited differences (variation) in drug metabolism and response” and pharmacogenomics as “the general study of all of the many different genes that determine drug behaviour.”

Figure 1 lists various definitions as given by different official bodies, and it is evident, that even now, the distinction between both terms is not completely exclusive. Indeed, the International Union of Basic and Clinical Pharmacology (IUPHAR) states that “...there is no internationally accepted consensus depicting any semantic differences between pharmacogenetics and pharmacogenomics.” However, while pharmacogenetics has been with us since Vogel’s first use of the term, pharmacogenomic research is mainly the fruit of the post-human genome sequencing era.

Pharmacogenetically-influenced drug responses

Inter-individual variations in drug responses may be influenced by a plethora of variables. These factors do not only influence therapeutic drug responses such as the degrees of efficacy and potency, but also the propensity to develop specific adverse effects. Some of these variables such as age, gender and body weight are well known, and are regularly factored into algorithms used for drug dosing. Pharmacogenetic profiling fills in the gap for another variable, and its relevance is particularly accentuated in those instances where it is a primary factor in influencing patient-to-patient variability. In it simplest form, pharmacogenetic data may be used to identify patients in whom a drug shows adequate efficacy, from patients in whom the same drug does not. This information may be used to assist the selection of which drug to administer to which patient, and to establish a relevant dosing schedule; in other words, to administer the right drug to the right patient at the right dose.

Table 2 shows a sample list of genes for which specific variants have been shown to exert an influence on particular drug responses. Changes in drug responses may be influenced by one particular genetic polymorphism alone, but more commonly, pharmacogenetically-influenced variations are the result of several gene variants interacting together and also with environmental factors, and this is one of the major challenges faced by researchers today.

Adverse drug reactions (ADRs) are estimated to be responsible for up to 7% of hospital admissions in the UK, with an estimated annual direct cost amounting to EUR 400 million. In addition, 10% of drugs which had been approved by the FDA between 1975 and 1999 were removed from the US market due to the appearance of new ADRs which were identified during the post-marketing surveillance stage. Besides known factors such as age, renal and liver function, disease status and lifestyle variables such as tobacco and alcohol consumption, genetic factors are also recognised to significantly modify the risk for development of ADRs. The classical example consists of genetic variation which decreases the activity of a drug metabolizing enzyme, resulting in a “slow-metabolizer” phenotype for a particular drug or group of drugs. Such patients exhibit higher blood concentrations when administered the drug at conventional doses, since they take longer to metabolize it, often resulting in gradual accumulation to toxic levels. Primary amongst the enzyme systems which have been studied in this respect, are the cytochrome P450 (CYP) group, of which there are more than 30 gene families in humans. One of the most studied CYP enzymes is CYP2D6 which is responsible for the metabolism of more than 100 drugs, which derive from diverse pharmacological groups. Examples of these include propranolol, flecainide, amitriptyline, nortriptyline, clomipramine, fluoxetine, haloperidol, thioridazine, codeine, debrisoquine, dextromethorphan, phenformin and tramadol. The CYP2D6 gene exhibits significant variability, and more than 75 alleles have been identified to date. Some of these produce an enzyme with normal activity, some alleles produce an enzyme with high activity and some
produce a low-activity CYP2D6 enzyme. In addition, individuals with multiple copies of functional CYP2D6 genes have been described, with resultant high enzyme expression and high CYP2D6 metabolic activity. Patients may be classified as poor, normal, rapid or ultrarapid metabolisers with respect to CYP2D6 metabolic activity, and this may have significant clinical implications. For example, the doses of nortriptyline required to attain a therapeutic response, may vary by over 20-fold between poor and ultrarapid CYP2D6 metabolizers. If poor metabolisers are administered “normal” doses, they are more likely to develop ADRs due to slow elimination with consequential potential accumulation, while conversely, ultrarapid metabolisers may not show any therapeutic response at all.18

Other pharmacogenetically-related ADRs may be related to membrane transporter proteins. The Adenosine triphosphate-Binding Cassette (ABC) genes code for a number of transmembrane proteins which are responsible for translocating drugs across extra- and intracellular cell membranes. Examples of such drugs include anticancer drugs, digoxin, immunosuppressants and some antiretroviral agents. Digoxin bioavailability, for example, is known to be influenced by variants of the ABCB1 gene.19

Drug hypersensitivity may also be influenced by pharmacogenetic variation. For example, abacavir, an anti-retroviral drug used in the management of HIV infection, exhibits a five-fold greater risk of hypersensitivity in patients with the HLA-B*5701 allele, and some medical centres in the USA are today HLA-typing patients before prescribing the drug.20

**Personalized medicine and drug development**

The ultimate goal of pharmacogenetics and pharmacogenomics research is to enable prescribers to utilize a patient’s genetic data (pharmacogenetic profile) in order to enable the selection of the drug from the applicable therapeutic repertoire, which would exhibit the greatest efficacy and the least adverse effects in that particular patient, and the prescription of that drug at a dose that is appropriate for that patient; that is, *genotype-guided prescribing*, or as it has been more universally termed, *personalized medicine*.20 This goal, although often considered by the practitioner community to still be a distant vision, is advancing rapidly, and pharmaceutical companies are today already integrating pharmacogenomic aspects into the drug development process.

This integration raises issues of a commercial interest. The “niching” of drugs to selected genetic groups may restrict their potential markets, and may appear to disadvantage pharmaceutical companies. However, the identification, during drug development, of a genetically-determined target population in which the drug offers superior benefit than currently available medication, may potentially rescue an otherwise unmarketable drug into a marketable one. Additionally, phase III trials of such a drug, may fail to indicate its superiority, unless they are performed in a genetically-selected population.21

For what drugs may personalized medicine be expected to be available first? Several variables may influence this, but the following may offer some insight:

a) drugs which show a high inter-individual variation in efficacy and/or potency.

b) drugs which possess a narrow therapeutic window and have to be used in conjunction with therapeutic drug monitoring. Both the starting dose, as well as subsequent dosage adjustments may be made with greater accuracy, if the patient’s pharmacogenetic profile is included into the equation.

c) drugs which demonstrate a clinical effect only several days after initiation of administration. The risk of having to substitute such a prescribed drug for another due to ineffective clinical outcome, or of having to alter the dose of the same drug, several days after therapy has been initiated, may be

### Table 1: The terms pharmacogenetics and pharmacogenomics as defined by different official organisations

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Pharmacogenetics</th>
<th>Pharmacogenomics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nuffield Council on Bioethics, UK</strong></td>
<td>The study of the effects of genetic differences between individuals in their response to medicines.</td>
<td>The examination of whole genomes or substantial numbers of genes in order, for example, to identify putative targets for medicines or to identify large-scale differences in the patterns of gene expression in response to chemical compounds.</td>
</tr>
<tr>
<td><strong>The National Centre for Biotechnology Information (NCBI), USA</strong></td>
<td>The study of inherited differences (variation) in drug metabolism and response.</td>
<td>The general study of all of the many different genes that determine drug behaviour.</td>
</tr>
<tr>
<td><strong>Food and Drug Administration (FDA), USA</strong></td>
<td>The influence of variations in DNA sequence on drug response</td>
<td>The investigation of variations of DNA and RNA characteristics as related to drug response.</td>
</tr>
<tr>
<td><strong>European Medicines Agency (EMEA), UK</strong></td>
<td>The study of interindividual variations in DNA sequence related to drug response.</td>
<td>The study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.</td>
</tr>
<tr>
<td><strong>International Union of Basic and Clinical Pharmacology (IUPHAR), USA</strong></td>
<td>The science about how heritability affects the response to drugs. How the systematic identification of all the human genes, their products, interindividual variation, intraindividual variation in expression and function over time may be used both to predict the right treatment in individual patients and to design new drugs.</td>
<td></td>
</tr>
</tbody>
</table>
and of the drug can be predicted for a particular patient. This is especially important in diseases where optimum therapy has to be instituted as early as possible in order to optimize clinical prognosis.

d) drugs which are known to have the propensity to exhibit serious adverse effects, even if the incidence of such effects is low.

Regulatory issues
Currently both the Food and Drug Administration (FDA), as well as the European Medicines Agency (EMEA) regulations do not require pharmacogenetic data to be submitted as part of a new drug licensing application. However, the FDA is asking pharmaceutical companies conducting drug development programs to consider providing pharmacogenomic data to the Agency on a voluntary basis. In this respect, the FDA has recently established an Interdisciplinary Pharmacogenomic Review Group (IPRG) to review voluntary pharmacogenomic data submissions (VGDSs) and provide feedback to submitters, provide guidance to the relevant FDA reviewing divisions and work on ongoing pharmacogenomic data submission policy development.22

At the same time, the EMEA Committee for Medicinal Products for Human Use (CHMP) established the Pharmacogenetics Working Party (PgWP), which currently meets four times a year in London and of which Malta is currently a member. The primary PgWP’s mandate is to provide for a technical multidisciplinary forum to the CHMP pharmacogenetics experts network and applicants. It accomplishes this by hosting workshops and briefing meetings to share experience on pharmacogenetics-related issues, preparing, reviewing and updating guidelines for the preparation and assessment of the pharmacogenetics parts of regulatory submissions, providing advice to the CHMP on general and product-specific matters relating to pharmacogenetics and liaising with interested parties and providing advice, through the CHMP, to the European Commission on pharmacogenetics-related issues.23 Since their inception, the PgWP and the IPRG have established collaborative links between themselves, and have already had the opportunities to provide joint advice to pharmaceutical companies.

Interpretation and ethical aspects
The concept of pharmacogenetic testing carries significant ethical implications. Issues which may be affected include the design of research studies and clinical trials, the pricing of medicines, and the accessibility of pharmacogenetic information and the implications of population stratification based on this data. The following highlights some of the main issues discussed in this document.

Development of new medicines
The report encourages regulators to promote the collection and storage of samples derived from clinical trials such that they could be subjected to pharmacogenetic analysis either during the trial, or later. This approach could permit re-analysis of data based on pharmacogenetic profile stratification,

### Table 2: A non-exhaustive list of genes for which specific variants have been shown to have clinical implications for specific pharmacological therapies.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Drug affected</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>warfarin</td>
<td>Increased anticoagulant effects of warfarin</td>
</tr>
<tr>
<td></td>
<td>tolbutamide</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole</td>
<td>Peptic ulcer response to omeprazole</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>Prolonged sedation, toxicity</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Nortriptyline</td>
<td>Increased antidepressant toxicity</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>Decreased codeine analgesia</td>
</tr>
<tr>
<td>CYP3A4/3A5/3A7</td>
<td>tacrolimus</td>
<td>Decreased efficacy of tacrolimus in organ transplantation</td>
</tr>
<tr>
<td>Dihydropyrimidine dehydrogenase</td>
<td>Fluorouracil</td>
<td>Increased neurotoxicity</td>
</tr>
<tr>
<td>Glutathione transferase</td>
<td>Several anticancer agents</td>
<td>Increased response in breast cancer, more toxicity and poorer outcome in acute myeloid leukaemia</td>
</tr>
<tr>
<td>GSTM1, M3, T1</td>
<td>Mercaptopurine, thiouguanine, azathioprine</td>
<td>Increased haematopoietic toxicity</td>
</tr>
<tr>
<td>Thiopurine methyltransferase</td>
<td>UGT1A1</td>
<td>Irinotecan</td>
</tr>
<tr>
<td></td>
<td>ABCB1 (MDR-1)</td>
<td>Digoxin, HIV protease inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased digoxin bioavailability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased CD4 response in HIV-infected patients</td>
</tr>
<tr>
<td>β₂-adrenoceptor</td>
<td>β₂-adrenergic agonists (eg. salbutamol, terbutaline)</td>
<td>Decreased bronchodilation response</td>
</tr>
<tr>
<td></td>
<td>β₂-adrenoceptor</td>
<td>β₂-adrenergic antagonists</td>
</tr>
<tr>
<td>Gsα</td>
<td>β₂-adrenergic antagonists</td>
<td>Decreased antihypertensive effect</td>
</tr>
<tr>
<td>ALOX5</td>
<td>Leukotriene receptor antagonists</td>
<td>Less improvement in FEV₁ (forced expiratory volume in 1 second)</td>
</tr>
<tr>
<td>Serotonin transporter (5-HTT)</td>
<td>Fluoxetine and other anti-depressants</td>
<td>Decreased antidepressant response</td>
</tr>
<tr>
<td>Human leukocyte antigen (HLA)</td>
<td>Abacavir</td>
<td>Increased likelihood of hypersensitivity</td>
</tr>
<tr>
<td>N-Acetyl-transferase 2 (NAT2)</td>
<td>Isoniazid</td>
<td>Exaggerated drug response, toxic metabolites</td>
</tr>
<tr>
<td>Sulfonylurea receptor</td>
<td>Tolbutamide</td>
<td>Decreased insulin response</td>
</tr>
</tbody>
</table>
and could identify smaller groups in whom the trial results are more robust, and who would be better candidates for the medicine being tested. The issue of population stratification presents as a double-edged blade in terms of commercial development. Some potentially valuable new medicines may not be developed if, as a result of genetic stratification, the number of patients who would benefit is too small for the venture to be commercially viable. However, stratification may also enable some medicines to be developed that would otherwise have failed because the subgroup in which the medicine is effective can now be distinguished.

**Improvement of existing medicines**

Pharmacogenetics could be used to improve the prescribing of existing medicines, for example either by predicting individualized dosing and thus reducing the incidence of adverse reactions, or by restricting prescription to those patients likely to benefit. Some potential examples include clozapine and warfarin for which sufficient data exists to make these strong candidates. The Nuffield Council recommended that efforts should be made to encourage pharmacogenetic research on existing medicines, where there is reason to believe that such research could significantly improve efficacy or safety, and that funding and support should be made available within the public sector and public–private partnerships should be encouraged.

**Withdrawn medicines**

The most common reason for medicines to be withdrawn from the market once they have been licensed is the subsequent occurrence of serious adverse reactions, which were either unsuspected at the time of marketing authorisation or occur more frequently than was expected. If some adverse reactions can be explained by genetic variation, pharmacogenetic analysis might enable some withdrawn medicines to be reinstated, by restricting their licensed use to a genetically-defined group of patients. This may be especially relevant in cases where there is currently no alternative treatment available to replace a withdrawn medicine.

### Key Points

- The major aim of pharmacogenetic and pharmacogenomic research is to enable prescribers to administer the right drug to the right patient at the right dose, i.e. to enable the establishment of personalized medicine.
- Drugs which are strong candidates are those which (a) show high inter-patient variability, (b) have a narrow therapeutic window, (c) demonstrate a clinical effect several days after initiation of administration, and/or (d) may exhibit serious adverse reactions.
- FDA and EMEA do not mandate pharmacogenetic data submissions as part of a new drug licensing application, but both organisations recommend it and both have established expert committees to evaluate this data.
- In drug development, pharmacogenetic research may aid in the development of new medicines for specific genetically-defined groups, it may improve existing medicines by identifying the patients in whom they show the highest benefit and it may re-instate some withdrawn medicines by restricting their licensed use to a genetically-defined subgroup of patients.
- For some drugs, pharmacogenetic tests will not unequivocally delineate patients who would and would not benefit from their use, but would rather predict the likelihood of each patient’s response. Adequate training must be provided for clinicians and pharmacists to enable them to correctly interpret such tests and advise patients accordingly.

### Cost

The incorporation of pharmacogenetic studies in drug development, would be likely to influence the cost of the final product. This has pharmacoeconomic implications and might adversely influence cost-benefit issues, possibly also presenting a barrier to medicine access.

### Information, training and education

The results of a pharmacogenetic test may not be as easily interpretable as other clinical tests, and the way in which the data may be best used, may not be immediately evident. In a number of instances, pharmacogenetic tests will not draw a clear line between a patient being a responder / non-responder to a particular drug, but will rather predict the *likelihood* of that patient’s response. The prescriber may have to consider other factors besides pharmacogenetic data, while making a decision, especially when bringing dosage regimen into the equation. Adequate training must be provided for clinicians and pharmacists to enable them to interpret such pharmacogenetic tests correctly and to advise patients accordingly. The Nuffield Council recommended that such testing should not be made available directly to the patient but only to trained health care professionals. However, in the case of pharmacogenetic tests which are able to provide a clear cut responder/non-responder result, patients could be provided with the means to directly request such testing themselves. The selection of tests which could be made available in this way should be decided by the relevant Health Authority.

### Ethnicity

Particular genetic variation may often be clustered to specific ethnic populations. Although ethnicity alone should not be used as a replacement for a pharmacogenetic test, this situation could make the commercialization of some drugs only viable within certain ethnic groups. This could cause serious concerns where, for example, solely due to commercial interests, whole countries could be denied the availability of these drugs, even though specific individuals may test pharmacogenetically positive for their use.

### Drug licensing

Even if it will improve the likelihood of receiving a safe and effective treatment, some patients might have an aversion to taking a pharmacogenetic test, either, for example because it might become more difficult to obtain health insurance,
or because it might indirectly reveal information about a medical condition which cannot be effectively treated. A question arises regarding whether these patients will still have the option to receive treatment without taking an associated test, or whether the drug licensing conditions will mandate it. This may also be relevant in developing countries which do not have recourse to testing, thus effectively making any use of such a drug in these countries, fall under off-label prescribing. 

Use by insurers
Pharmacogenetic information could be of relevance to insuring companies, especially those providing types of healthcare insurance such as private medical insurance and long-term care insurance, as well as life insurers. Such genotyping may be used to classify individuals as “more expensive” or “less expensive” to treat and could be used to define premiums for people applying for policies, as well as to adjudicate claims in order to make decisions about payment to policy-holders. The Nuffield Council strongly advocates in favour of the setting up of regulations that would deny insurers any right to request genetic information.

Conclusion
Half a century from the Watson and Crick’s identification of DNA structure, and 5 years from the completion of the Human Genome Sequence, the implications of genetic research have infiltrated our daily lives. Pharmacogenetic-based individualized drug therapy aims to provide a safer and personalized therapeutic option for patients, with better clinical outcomes and disease prognosis. As new high throughput research methodologies are developed, and further automation is introduced into research laboratories, the development and commercialization of pharmacogenetic tests may become a reality sooner rather than later. Roses, in 2002 had already speculated that a pharmacogenetic test kit could be developed by a pharmaceutical company, validated and commercialized within a time frame as short as 2 to 3 years, and more recently, Lesko (2007) suggested that a pharmacogenetic kit could be commercialized for point-of-care use by the prescriber himself at a cost of only around USD0 per test. Now is the time for health care professionals to start seeking the knowledge and training that will prepare them for the introduction of pharmacogenetics/pharmacogenomics into the framework of pharmacological management and patient care.

References
Benzodiazepines: benefits versus risks

Lorna Marie West BPharm(Hons), MSc(Clin Pharm)Aberdeen
Senior Clinical Pharmacist, St. Luke’s Hospital, G’Mangia, Malta
Email: lorna.m.west@gov.mt

Key words: benzodiazepine, dependence, withdrawal, tolerance, anxiety

Benzodiazepines act on the central nervous system and can be prescribed for various medical conditions. They are usually classified by their duration of action. Patients using long-term benzodiazepines are at risk of dependence and tolerance. Benzodiazepines may also worsen or mask symptoms of depression and may cause cognitive and psychomotor impairment. Therefore, benzodiazepines should not be prescribed in the absence of a clear indication. When prescribed, benzodiazepines should be prescribed in as low a dose as possible and long-term patients should be reviewed regularly.

Introduction

Benzodiazepines are drugs which depress activity in the part of the brain which controls emotion by promoting the action of a chemical called gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, thus preventing excessive brain activity that causes anxiety. Benzodiazepines can be prescribed for various medical conditions which include anxiety, insomnia, alcohol withdrawal, seizure control, muscle relaxation and to induce amnesia for uncomfortable procedures. They can also be given before administration of an anaesthetic, e.g. prior to surgery. Benzodiazepines act on the central nervous system resulting in sedation and muscle relaxation, and lower anxiety levels. Benzodiazepines are usually classified by their duration of action as indicated in Table 1.

Uses of Benzodiazepines

**Anxiety**

Benzodiazepines should be prescribed primarily for the short-term relief of severe anxiety when this is resulting in significant distress or problems in social functioning. Benzodiazepines are effective anxiolytic drugs having an immediate onset of action, with their maximum benefit shown in the first few weeks of treatment. Thus they may offer a period of respite whilst other more indicated treatments such as antidepressants have time to act. Long-term prescription of benzodiazepines may be considered desirable in certain circumstances when other alternatives are considered less appropriate than the use of benzodiazepines. This may be in conditions such as chronic treatment-resistant anxiety or in patients who have confirmed dependency and are unable to withdraw successfully. Rarely, benzodiazepines may be prescribed in the long term as maintenance treatment in patients who would otherwise consume illicit benzodiazepines. In situations where anxiety is complicated by other illnesses such as schizophrenia, the risk of dependence may be considered acceptable because of the severity of the other disorder. Benzodiazepines may also be used as adjunctive treatment in the initial management of acute mania where sedation is a priority. In other instances there is much less evidence to support the use of benzodiazepines.

**Depression**

Depression is not a primary indication for prescribing benzodiazepines. Benzodiazepines may only be prescribed for depression if the latter is accompanied by anxiety or severe distress for short-term relief when the patient is subject to extreme distress. They do not have a specific antidepressant effect, and may offer early symptomatic relief while antidepressants have time to act, or cover the initial increase in anxiety that may occur when some antidepressants are prescribed.

**Sleep**

Benzodiazepines are effective hypnotics for the short-term treatment of insomnia if given in sufficient doses. Again, they should be used intermittently for 2 to 4 weeks and at the lowest dose while more appropriate long-term treatments are instituted, if the problem is long-term. Primary causes of insomnia, such as depression or substance misuse, should be excluded.

**Anticonvulsant and muscle relaxant actions**

Benzodiazepines have anticonvulsant and muscle relaxant properties. These are often valuable, particularly in the emergency treatment of epilepsy and the management of spasticity or muscle spasms.

**Excitement, agitation and severe psychotic disturbance**

Patients with excitement, agitation and severe psychotic disturbance may be prescribed short-term benzodiazepines to obtain rapid tranquillisation or as an adjunct to their antipsychotic drugs. The dose and duration of such treatment needs to be monitored closely.
Risks of Benzodiazepines

Dependence

Long-term use of benzodiazepines can result in dependence. Dependence on benzodiazepines is mainly manifest by withdrawal symptoms and even seizures on abrupt cessation. These symptoms may sometimes be prolonged and they may be hard to distinguish from other anxiety-related disorders such as panic disorder. Symptoms usually develop after three days of benzodiazepine cessation, although they can appear earlier with short-acting varieties. Short-acting benzodiazepines are more likely to lead to a withdrawal syndrome than long-acting ones. Therefore, to reduce the risk of dependence on benzodiazepines, these should not be prescribed regularly for longer than one month, and ideally be given on as-required basis and intermittently every few days.

Tolerance

Tolerance can develop with continued use of benzodiazepines. Tolerance to the hypnotic effects tends to develop rapidly whereby patients are initially relieved from insomnia, but this is followed by a gradual loss of efficacy. Tolerance to the anxiolytic effect develops at a slower rate, but there is little evidence to indicate that benzodiazepines retain their efficacy after four to six months of regular use.

Depression

Benzodiazepines may worsen or mask symptoms of depression. Consequently, this may deny the patient the opportunity of effective antidepressant medication. Moreover, it may result in disinhibition which may lead to suicide attempts. Therefore, a benzodiazepine should only be prescribed for a brief concomitant period with an effective antidepressant, such as a tricyclic antidepressant (TCA) or a selective serotonin re-uptake inhibitor (SSRI), followed by a clinical review within 2 weeks. Augmenting an antidepressant with another antidepressant should be considered for patients whose depression is treatment resistant and who are prepared to tolerate side effects. However, there is insufficient evidence to recommend the use of benzodiazepine augmentation of antidepressants.

Misuse

Death rarely results from benzodiazepine abuse alone. However, a proportion of the population may abuse benzodiazepines as part of a wider drug and alcohol problem. Therefore, doctors should be aware that medications they prescribe may fall into the wrong hands. Maintenance benzodiazepines given to addicts are often used to supplement illicit sources.

Cognitive impairment

Benzodiazepines may cause cognitive impairment, mainly involving memory disturbance and subtle learning impairment. Cognitive impairment may not allow patients to make an optimum response to a situation which they may be facing. In cases of loss or bereavement the psychological adjustment to this trauma may also be inhibited by benzodiazepines. On the other hand, short-term symptomatic relief of benzodiazepines may aid the natural healing process.

Disinhibition

Extreme caution should be used in prescribing benzodiazepines in patients with severe personality disorders. Studies have shown that use of benzodiazepines in such patients may increase the incidence of suicidal behaviour. Moreover, combination with alcohol is common and dangerous. The use of benzodiazepines in this category of patient may facilitate aggressive behaviour both towards the self and others.

Psychomotor impairment

Higher doses of benzodiazepines may cause psychomotor impairment which could affect activities such as driving and operating machinery. Therefore, when starting benzodiazepines a low dose should be given initially. Furthermore there is a particular problem with the elderly, who are more sensitive to benzodiazepine effects and who metabolize long-acting benzodiazepines slowly. There is a build-up of drug over time and this may result in chronic intoxication and falls resulting in fractures.

Sleep

Studies have shown that patients who have taken benzodiazepines for period in excess of 4–6 months have become, inadvertently, dependent and experience withdrawal insomnia. Psychiatric disorders such as anxiety, depression and abuse of drugs and alcohol are common causes of chronic insomnia. Chronic insomnia is rarely benefited by hypnotics such as benzodiazepines. Instead the underlying psychiatric complaint should be treated. Therefore, the Committee on Safety of Medicines (CSM) suggests that benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.

Recommendations

Studies still show a continued high prevalence of benzodiazepine use despite the well known adverse effects.

---

Table 1: Duration of action of benzodiazepines

<table>
<thead>
<tr>
<th>Ultra-short acting</th>
<th>Short-acting</th>
<th>Intermediate-acting</th>
<th>Long-acting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t½ less than 6 hours</td>
<td>t½ 6-24 hours</td>
<td>t½ greater than 24 hours</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Zopiclone</td>
<td>Alprazolam</td>
<td>Diazepam</td>
</tr>
<tr>
<td></td>
<td>Zolpidem</td>
<td>Lorazepam</td>
<td>Flurazepam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temazepam</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Withdrawal guideline for patients on benzodiazepines

1. Transfer patient to equivalent daily dose of diazepam preferably taken at night
2. Reduce diazepam dose every 2-3 weeks in steps of 2 or 2.5mg; if withdrawal symptoms occur, maintain this dose until symptoms improve
3. Reduce dose further, if necessary in smaller steps (diazepam 500 micrograms to 2.5mg)
4. Stop completely; time needed for withdrawal can vary between patients
When a patient complains of insomnia one should first consider non-pharmacological measures, such as avoiding caffeine-containing products late at night, exercise during the day, identify and avoid, if possible, the cause of the insomnia. Benzodiazepines should only be prescribed for insomnia for short-term use in accordance with their licensed indications. If insomnia continues to be a problem, one may opt to prescribe a short-term non-benzodiazepine hypnotic, for a maximum of 2 weeks’ duration. Whilst withdrawing benzodiazepines, the patient will need other supportive measures such as counseling and relaxation techniques. If a patient is benzodiazepine and opioid dependent, both drugs would not normally be withdrawn simultaneously. The opioid dose is kept stable until full withdrawal from the benzodiazepine has been attained.

of benzodiazepines discussed above and the availability of safer and effective alternatives. From these studies it was shown that primary care physicians are averse to addressing the public health problem of benzodiazepine overuse in the elderly. Researchers found contraindications, including falls and depression, in 75 per cent of those given benzodiazepines. Therefore, repeat prescriptions could be a cause of benzodiazepine overuse. Doctors’ attitudes generally conflict with practice guidelines and they complain of a lack of training in constructive strategies to address this problem. Hence, the following recommendations are being made:

1. Benzodiazepine should not be prescribed in the absence of a clear indication. Benzodiazepines should be prescribed in as low a dose as possible to afford symptomatic relief and patients should be advised of the risk of dependence associated with long-term use. Patients should also be advised to obtain their prescriptions for benzodiazepines from the same doctor, wherever possible, so that risk of dependence may be monitored. In addition patients should be advised on possible adverse effects such as drowsiness, which may have an effect on driving or operating machinery.

2. When prescribing benzodiazepines long-term patients should be reviewed. This should include a review of the indication for continued use of the benzodiazepine, the dosage regime and any possible side-effects.

3. Benzodiazepine reduction and cessation should be with the patient’s consent and co-operation.

4. Even after the short-term use of benzodiazepines, it is advised that a tapering-off regime (i.e. at least 2 weeks at reduced dosage) should be used to minimize rebound phenomena. After longer use this reduction period may have to be extended, sometimes to several months in extreme cases.

5. Benzodiazepine tapering-off may be facilitated by changing patients to long half-life medications, such as diazepam, and then slowly reducing the dose. A suggested withdrawal guideline for patients who have difficulty in stopping benzodiazepines is shown in Table 2.

Conclusion

Benzodiazepines may be prescribed safely and effectively for the short-term treatment of anxiety and insomnia and can also be used for some forms of epilepsy and spasticity. Dependence is now recognized as a significant risk in patients receiving treatment for longer than one month and is often extremely difficult to treat. Therefore, doctors have to examine the benefit: risk ratio of continued prescription in each individual early in treatment, so that if dependence occurs, it is anticipated by doctor and patient alike.
Personal experiences of health and illness on the web: A resource for patients, carers and health professionals

People are becoming savvier as health consumers when faced with the need to make decisions. They are turning to the internet for both factual and experiential information. DIPEx, an award-winning, electronic, multi-media resource of personal experiences of health, illness and related issues on the web, addresses this need with evidence-based information alongside video, audio and written interview clips that identify issues that matter to people. The website is freely available 24 hours a day providing support for patients and their families, friends, carers and health professionals from the personal perspective.

People need relevant and reliable information quickly

People have to make decisions about health at various stages throughout life, for example when they or a family member become ill or when they are about to become a parent. At such times most say that they want up-to-date information about the condition and care or treatment options. They also want to hear what it is like from others who have been through the experience, how to tell family and friends, where to find support and what questions to ask their health professionals.

In addition, they say that they want their health professionals and others to really understand what they are going through. More and more they are turning to the internet for the information and support they need.

DIPEx can help

DIPEx (www.dipex.org), an award-winning, electronic, multimedia resource about people’s experiences of health, illness and related issues, helps address these needs by providing up-to-date, evidence-based information (often linked to other sources), answers to questions that the people have raised themselves and information about support groups. It also provides links to other resources such as the Cochrane Collaboration, the UK National Electronic Health Library and Cancerbackup. However, the unique and most powerful part of the DIPEx resource is the video, audio and written accounts of peoples’ lived experiences.

DIPEx is available on the internet; some of the modules on the various conditions are also available on DVD. It is of use to patients, carers and health professionals, including researchers, teachers and students. It is completely independent from commercial interests and information. It aims to describe the widest possible range of peoples’ health-related experiences and to be an information-rich resource for people faced with health issues and those who care for them.

How DIPEx is built

DIPEx is the result of a series of stand-alone qualitative research studies on a wide and expanding range of health

Key words: internet patient experiences, DIPEx, qualitative research, health information, decision-making

Kath Ryan1 BPharm, PhD(Otago)
Andrew Herxheimer2 MB, FRCP

1Reader in Maternal & Perinatal Research, Institute of Health & Community Studies, Bournemouth University Royal London House, Bournemouth, UK
Email: kryan@bournemouth.ac.uk

2Emeritus Fellow, UK Cochrane Centre, UK

Issue 13  Summer 2007
related topics such as various cancers, cardiovascular disease, mental health, neurological conditions, epilepsy, young people’s health experiences, women’s health and parenting (see Table 1). The qualitative studies have UK multi-region ethics committee approval.

For each study an Advisory Panel of experts in the field, including academic researchers, health professionals, policy makers and lay representatives, is set up to help recruit participants, to guide the researcher and to review the analysis of the interview data. A maximum variation sample of around 40 people is recruited to capture as wide a variety as possible of experience, age, gender, ethnicity, socioeconomic status, domestic setting, and treatment choice if applicable. Participants are recruited through primary and secondary care, support groups, and informal networks such as internet discussion groups.

Interviews are generally conducted in people’s homes and recorded on both digital video and audio tapes. After the interview, participants are sent a verbatim transcript and can choose to remove any sections they wish before granting DIPEx permission to use the interview for the website, teaching and research publication purposes. At this point participants also specify in what format(s) their interview may be used (video, audio or written only). The dataset for each study is analysed thematically with the aid of computer-assisted qualitative analysis software. Each theme or topic is written up as a brief summary that captures the range and variation of experience and is illustrated by video, audio or written extracts from the interviews.

How DIPEx can help

Patients, carers, and members of the public who access the DIPEx website can see and listen to other people talking about their experiences. They will find someone with a similar experience with whom they can empathise. They will also gain practical and emotional support for what they are going through and will be able to identify what they need to know and understand, and what questions to ask their health professionals.

In spite of initial opposition to people seeking health information on the internet, the informed health consumers are now often viewed as desirable12, even if many don’t tell their doctor that they have accessed information from the internet. It has even been suggested that health professionals may give people ‘information prescriptions’ directing them to appropriate websites such as dipex.org .13

Besides directing patients to the website for information, practical and emotional support, health professionals can access DIPEx to gain insight into the non-clinical aspects of what it is like to be faced with a health decision or to live with a health issue or concern. The video clips of personal experiences on the website can be used to enhance shared decision-making between professionals and the people for whom they care. Furthermore, many professions are beginning to use DIPEx for continuing professional development.

The DIPEx website also provides a rich resource for undergraduate and postgraduate teaching where it has been used in teaching clinical communication and qualitative research methods to a variety of health professional students and health care workers. We intend to develop a range of formal teaching modules from the database.

Other users of the DIPEx site include researchers who have used the data for a variety of secondary analyses, including sociolinguistics, condition-specific analysis of a data set and thematic analysis across several collections.14,15 Because the DIPEx website is freely available to all, it provides a means for patients and other representatives on health services committees to access a broad range of experiences and deepen their understanding of a variety of perspectives.

How DIPEx has grown

DIPEx was the brainchild of Ann McPherson and Andrew Herxheimer, both health professionals who had undergone an

| Table 1. List of health related topics on DIPEx website |
|---------------------------------|---------------------------------|
| Category                        | Illness or Condition            |
| Cancer & screening              | Breast cancer                   |
|                                 | Breast screening                |
|                                 | Cervical cancer                 |
|                                 | Cervical screening              |
|                                 | Bowel cancer                    |
|                                 | Lung cancer                     |
|                                 | Ovarian cancer                  |
|                                 | Prostate cancer                 |
|                                 | PSA Testing                     |
|                                 | Teenage cancer                  |
|                                 | Testicular cancer               |
| Chronic health issues           | Chronic pain                    |
|                                 | Rheumatoid arthritis            |
|                                 | HIV                             |
| Young people’s experiences      | Sexual health of young people aged 18-25 |
|                                 | Teenage cancer                  |
|                                 | Diabetes Type I in young people |
| Women’s health, pregnancy & screening | Pregnancy                  |
|                                 | Antenatal screening             |
|                                 | Ending a pregnancy for fetal abnormality |
|                                 | Screening for sickle cell, beta thalassaemia |
|                                 | and other variants              |
| Heart disease                   | Breastfeeding                   |
|                                 | Parents of children with congenital heart disease |
|                                 | Heart attack                    |
|                                 | Heart failure                   |
|                                 | High blood pressure             |
| Immunisation                    | Immunisation                    |
| Intensive care                  | Intensive care                  |
| Living with dying               | Living with dying               |
| Neurological                    | Epilepsy                        |
| Mental health                   | Carer’s of people with dementia |
|                                 | Depression                      |
Acid Erosion. A way forward.

Protection now comes from ProNamel with Microhardening.

New from Sensodyne: a dentifrice that protects your at-risk patients from the damaging effects of erosive tooth wear, an emerging clinical issue as its prevalence increases along with the popularity of acid-containing diets.

ProNamel remineralises and microhardens softened enamel due to its maximised fluoride formula. Low abrasivity (REA) also helps protect dentine and enamel from the wear and tear of daily oral hygiene. As you would expect from a Sensodyne toothpaste, ProNamel helps to relieve twinges and avoid further dentine hypersensitivity, while offering effective cleaning and freshening when used twice a day, every day.

So when you identify the signs of acid erosion, you can complement your regular chairside care and advice with daily effective homecare and protection. Recommend ProNamel from Sensodyne.
illness experience in the mid 1990s. They recognised the value of hearing from others about what it was like to be ill and to be treated. Since those early days, DIPEx has grown until, by summer 2007, 38 conditions will have been completed, with a further 11 studies underway. Collections are planned for over 100 other conditions, but growth will depend upon funding since each module is funded by a mixture of public and private non-commercial sources (for details see website). DIPEx is a registered charity with a research group based in the Department of Primary Health Care at the University of Oxford. Some projects are done in collaboration with other research groups and there is international interest in setting up DIPEx-like projects in other countries.

**How could pharmacists and other health professionals in Malta use DIPEx?**

Since in Malta one of the official languages is English, most people could use DIPEx. If pharmacists know about it and are aware what diseases and problems it deals with, then they can share that not only with patients and customers, but also with their assistants in the pharmacy and their colleagues in the other health professions. That could lead to many more fruitful conversations between patients and professionals.

We would ourselves also love to know what patients and professionals in Malta think about DIPEx - what seems specially useful in Malta, what they like, what they find difficult, what improvements they suggest.

### References

1. Dickinson D, Raynor DKT. Ask the patients - they may want to know more than you think. BMJ 2003; 327:861.

### Event

The Institute of Health & Community Studies, Bournemouth University, UK and The School of Pharmacy, University of Auckland, NZ invite you to **Globalisation, Pharmacy and Medicines**

15th International Social Pharmacy Workshop
8-11 July, 2008

Cathorffe Hotel & Resort Queenstown Lakefront, New Zealand

Abstracts will be called for from July, 2007
Early bird registration from August, 2007
Medical, Laboratory Equipment & Supplies

- Sourcing and Supply of all types of Medical and Laboratory equipment.
- Turnkey contracting for Hospitals, Industrial and Clinical laboratories.
- Analytical Equipment for R&D facilities and Quality Control departments.
- Tailor made solutions with guaranteed Quality Maintenance service.
- Medical Products for Home use for better quality of life especially for senior citizens and disabled persons.
- Trained staff always at hand to help and advise you.

Technoline
Serving Medicine and Science since 1978

51, Edgar Bernard Street, Gzira GZR 1703 - Malta
Tel: 21 344 345   Fax: 21 343 952   admin@technoline-mt.com

Showroom: 68, Nazju Ellul Street, Gzira
Opening Hours: 8.00am to 5.00pm - Monday to Friday
www.technoline-mt.com
ROTARIX™ Abbreviated Prescribing Information

Refer to SPC before prescribing. Rotarix™, live attenuated human rotavirus (501441 strain) oral vaccine. 

Uses: Active immunisation of infants from 6 weeks of age against gastroenteritis due to rotavirus infection.

Dosage and administration: Two oral doses. First dose can be administered from 6 weeks of age. Minimum interval of 4 weeks between doses. Vaccination course must be completed by 24 weeks of age. RotaTeix is for oral use only. Rotarix should under no circumstances be injected.

Contraindications: Hypersensitivity to the active substance or of the excipients. Hypersensitivity after previous administration of rotavirus vaccines. Previous history of intussusception. Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception. Subjects with immunodeficiency. Asymptomatic HIV infection is not expected to affect the safety or efficacy of Rotarix™. However, in the absence of sufficient data, administration of Rotarix™ to asymptomatic HIV subjects is not recommended. Administration of Rotarix™ should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not an contraindication for immunisation. Administration of Rotarix™ should be postponed in subjects suffering from diarrhoea or vomiting.

Precautions: Administer with caution to individuals with gastrointestinal illness or growth retardation. Administer with caution to individuals with immunodeficient close contacts. Do not inject. Rotarix is for oral use only.

Interactions: No interactions with co-administered paediatric vaccines.

Pregnancy and Lactation: Not intended for use in adults. Breastfeeding may be continued during the vaccination schedule.

Adverse reactions: Irritability, loss of appetite, diarrhoea, vomiting, flatulence, abdominal pain, regurgitation of food, fever, fatigue. Legal category: POM. Presentations: Pack size of 1 glass container of powder plus 1 oral applicator syringe of solvent to make up 1 dose (1ml) of oral suspension.

Further information and full prescribing information: GlaxoSmithKline Malta Tel: 21 238131 Date of preparation: December 2006

"Rotarix™ provides early protection from rotavirus gastroenteritis, pass it on."
Health perceptions and adherence to diet

Josianne Scerri1 BEd (Hons), MEd, MI Biol  
Eamonn Ferguson2 BSc, PhD, CFychol, FRSH, AFBPsS  
Christian A. Scerri3 MD, PhD, MMPath

1Doctoral Research Student, Risk analysis, Social processes & Health group, University of Nottingham, UK  
2 Professor of Health Psychology, Risk analysis, Social processes & Health group, University of Nottingham, UK  
3 Lecturer, Institute of Health Care, University of Malta, Msida, Malta  
Email: josianne.screrri@um.edu.mt

Key words: words: health perceptions, self-regulation, coeliac disease, adherence

Advances in the medical and technological field have greatly extended the life-expectancy of individuals with chronic conditions. However, such individuals may still experience difficulties in various domains such as in adjusting to their condition and in adhering to a recommended treatment regimen. Hence, one potential role of research on health perspectives is to provide information on factors which contribute to the favorable management of a chronic condition. This paper will utilize Leventhal’s self-regulation model1 in order to explain plausible cognitive factors that may have an influence on adherence to a diet regimen.

Introduction

Many persons in their mid and late adult life are confronted with one or more chronic disease.2 These diseases may pose various challenges and threats to the individual and many times to members of his/her own social network. An example of a possible challenge faced, is the preparation of and adherence of the individual to a strict diet. As health professionals it is of major concern that various individuals do not adhere fully to their diet, even though it is a vital component of their treatment regimen. In order to understand such illness behaviours one must appreciate that persons with chronic conditions constantly weigh how necessary a prescribed diet is perceived to be, relative to any concerns they may have in following such a diet.3 Moreover, their health perceptions regarding a treatment regimen is built up and influenced by various sources such as personal experiences, past experiences with the disease, information obtained from contact with others (e.g: health professionals, friends, relatives), as well as the media, cultural and social influences about health and illness and the internet.4,5 Various health models have been proposed to explain non-adherence to treatment. In this article, we will be utilizing, the self-regulatory model of illness behaviour,1,4 as a framework to comprehend non-adherence to treatment. This model will be adopted due to its special relevance in explaining and predicting patient adjustment and adherence to treatment regimens1 and will be described in the following section.

The Self-Regulatory model

This model posits that individuals are active agents who form illness representations regarding their condition. These perceptions and beliefs are dynamic and changing as the individual tries to understand and regulate his/her condition. Moreover, these health representations play an important role in influencing and regulating the coping strategies adopted, and via coping, various outcome measures such as adherence to treatment and emotional reactions.4 Research emanating from a number of different medical conditions implicates that these health perceptions consist of seven cognitive dimensions. The first dimension, identity is concerned with the illness label (e.g: celiac) and its concrete symptoms (e.g: feelings of bloatedness). The time-line dimension is divided into an acute/chronic subscale and also a cyclical subscale which incorporates whether the person perceived his/her condition as cyclical in nature. The consequences dimension comprises the individual’s perceptions regarding the short and long term impact of the disease on his/her life as well as the individual’s belief on illness severity. The causal dimension is based on the individual’s perceptions on the potential causes of the illness. Personal control refers to beliefs about one’s own ability to control symptoms whilst treatment control is an indication of the patient’s belief on treatment effectiveness in controlling their illness. As a measure of the emotional impact of the condition, an emotional representation dimension was included. The illness coherence dimension measures the individual’s perceived overall understanding of their illness.

These various illness dimensions, which have been put forward in the self-regulation model will be exemplified in this paper using the coeliac condition as an example. This chronic condition is one which requires
strict adherence of the individual to a gluten-free diet. However, it is imperative to add that the points raised in this article could also be applied to any other chronic condition which requires adherence to a prescribed diet.

Types of non-adherence
Non-adherence to treatment can be categorized as shown:

i) unintentional: this occurs when the individual wishes to follow the diet but is prevented from doing so due to some unintentional factor, such as poor comprehension of diet requirements;

ii) intentional: when the individual takes a voluntary decision not to follow their prescribed diet to various degrees.

Aim
The aim of this paper is to illustrate how the self-regulation model provides a framework to understand possible causes of non-adherence to diet in coeliac patients.

Method
Participants
In order to investigate these illness dimensions, a total sample of 40 Maltese adolescent and adult coeliac individuals were interviewed. These participants formed part of a larger sample (N=197) of patients having a range of chronic genetic conditions and who participated in a 3 year longitudinal study by the first author for her doctoral requirements. Eligibility criteria included that the diagnosis of the coeliac condition was confirmed by a small intestinal biopsy, that the individuals were above 12 years old (adolescents) and that they had been diagnosed with their condition for at least 6 months.

Procedure and measures
The following procedure was adopted to recruit coeliac individuals. Both health professionals and the coeliac support groups were contacted. The participant was first approached by the health professional or a key member of the coeliac support group and the nature and purpose of the investigation was explained to the individual. In all cases, the rights of the person/s to decline participation was/were respected. Selection of individuals from the list of members of the coeliac support association was computed by giving each member a number (1 to N, where N is the total number of members in the association) and using a computer program to randomly select the number of participants required. Participants demonstrating a willingness to participate in the study were then approached by the first author. It was decided to contact them initially by telephone rather than by written contact as any queries could be immediately clarified.

The coeliac individuals were administered a questionnaire designed by the first author to examine demographics, causal attributions for disease and lifestyle changes. The construct validity (determined by factor analysis) and reliability (determined from Cronbach alpha values, test-retest reliabilities and inter-item correlations) of this instrument have been established. The items in the questionnaire were read out by the first author and the patients provided written responses. All the interviewing was completed in the location requested by the patient, to ensure that the participant would feel at ease. It was carried out by the first author in Maltese or English depending on the request of the participants. Moreover, for adolescents under the age of 16, parental consent to participate in the study was first obtained and the interview was held in the presence of a family member. The purpose behind the study was explained to the subjects and they were instructed that their responses would remain confidential. The whole procedure lasted on average about 60 minutes.

For the purpose of this paper, quotes dealing with treatment adherence were obtained from patient responses to the question on the impact of their illness to their lifestyle. This selection procedure was done however, keeping the framework of the self-regulation model in mind.

Data analysis
The written responses of patients regarding the impact of the coeliac condition, (if any), on their life-style was read by the first author and analyzed for meaningful segments. These segments (key words, phrases and explanations) were highlighted and then allocated into themes.

Results and discussion
Of the participants in this study, 75% were female. The mean age of the participants was 42.15 years (SD=15.45, range=12-78) and their mean illness duration was 6.15 years (SD= 4.57, range=1-37).

Life style thematic categories
There was a 100% inter-rater agreement regarding the following life-style thematic categories: social (e.g: eating out at the same restaurant), emotional (e.g: feeling different from their peer group; feeling upset that adherence to diet had not prevented the development of further complications); management of coeliac condition (e.g: eating gluten free food and following a more ‘natural’ diet); physical (e.g: feeling healthier) and spiritual (e.g: stopped attending mass). Then individual patient quotes on adherence, falling under these life-style themes, were then selected on the basis that they related to the illness representations that are listed below.

Illness perceptions
The following examples illustrate the major dimensions of illness representations and how patient’s perceptions on the impact of their illness may influence their adherence. Example quotes for the various illness representation dimension are provided.
i) Illness coherenece: is a term indicative of one’s perceived understanding of a chronic condition. Various studies such as that by Ljungman and Myrdal,10 have demonstrated that a better knowledge of the coeliac condition is related to an increased adherence to a gluten-free diet. Thus, an incomplete picture of the coeliac condition and required dietary treatment may lead to less accurate beliefs about one’s prognosis. This may ultimately have an impact on strict adherence to diet.

ii) Timeline: represents the perceived duration of an illness. The coeliac condition is a chronic condition for life. Thus, if an individual perceives it to be an acute (short term) condition or one cyclical in nature (e.g., seasonal), the individual him/herself may be tempted to doubt the necessity of following a strict diet for life. Such a case was documented in a study by Meyer, Leventhal and Gutman,11 on a sample of people with chronic hypertension. It was observed that those individuals who considered their chronic condition as acute in nature tend to adhere less to the treatment regimen. The following example illustrates this point:

“I keep a list attached to the fridge with items that I am expected to avoid, but I still cheat frequently especially by eating ‘normal’ bread. I then begin to itch very badly but this can be helped by taking these pills which stop me from itching. I get very upset but my sister-in-law told me her friend’s son was coeliac as a child but then grew out of it. I am hoping that this will happen to me too.” (Female, 39 years; diagnosed 1 year ago).

iii) Treatment control: represents the perception that following one’s treatment is beneficial. One manner to evaluate the effectiveness of a treatment is based on whether there has been an amelioration of symptoms experienced or not. Many coelicals during the interview cited a feeling of being ‘rejuvenated’, ‘now following a natural diet’ or ‘feeling healthier’, after being placed on a gluten-free diet. Such individuals may perceive adherence as a necessary measure that has provided them with a new lease of life. However, in other cases the individual may believe that the diet is ineffective. This may arise for example, when another chronic condition appears such as diabetes or psoriasis (in addition to the coeliac condition) or when the level of antigliadins in the blood is higher than the required norm- even though the person is allegedly following the diet. The following quote exemplifies these points:

“I have always followed my diet. At home, they accuse me of being too obsessed, as I am preoccupied with avoiding contamination of my utensils and food. Then when I go for my check-up, the level of antigliadins is found to be high. So I ask myself how could it be? I think that there is more to it than the doctors tell us, they do not know everything yet about our disease” (Female: 52 years; diagnosed 3 years ago). In the quote cited above, the participant perceived that adhering to the diet was not effective in preventing the expression of symptoms normally associated with non-adherence. She felt confused and felt that there was some vital piece missing from the jigsaw puzzle, which represented the established present day knowledge on the coeliac condition. By adhering to the treatment, this participant was not receiving the desired outcome (acceptable blood antigliadin levels) that she expected considering her intense efforts to adhere to the diet.

iv) Personal control: represents a belief in one’s personal ability to control a chronic condition. In fact, one may find individuals who emphatically stress the importance of a gluten-free diet and yet they do not perceive themselves as capable of exerting the control needed to follow it. The following quote illustrates this point:

“When I am cooking pasta for the rest of my family, I taste some of their pasta and then I spit it out. Like that at least I can enjoy the taste and then I spit it out so that I will be causing the least possible harm to my body. I do it every time.” (Female, 55 years; diagnosed 1 year ago). In such cases as shown in the previous citation, the individual is aware that she is causing harm to herself however the problem lies in her perceived inability to exert the necessary control to follow a strict gluten-free diet.

v) Consequences and emotional representations: this term encompasses the perceived impact (psychological, social, physical and economic) of the coeliac condition on the individual. Some persons view their condition as having a positive impact on their life. For example they will cite reasons such as ‘feeling healthier’. Conversely, other individuals may quote not following a strict gluten-free diet due to for example, its impact on their social/emotional life. The quotations cited below amplify this point:

“I go out with friends and I am always making up excuses, as I do get people asking me to take a bit of this or that. Even when I tell them no, they still do not get the point. I do not feel that I should tell them that I am coeliac, as it is a personal matter. Once in a while I get tired resisting and I then I just give in” (Female, 18 years; diagnosed 5 years ago). As shown in the above example, the individual has the required knowledge of her condition but opposing the constant good intentions of her colleagues (as they do not know that she is coeliac) is proving distressful.

The following quote gives another example of the consequences (spirital impact) of following a diet regimen. One must appreciate that till some time ago, gluten-free hosts for Holy Communion, were not yet available on the island and coeliac individuals would receive wine instead. This normally involved ensuring that the priest was aware of their condition, as well as having to be one of the first or last persons out in the church aisle in order to receive the wine in a special container or a spoon. The following quote illustrates the experience of one lady:

“When I attended church, I used to go up before everyone else to receive the wine instead of the host. One day a...
group of youngsters began laughing and calling me a drunkard. My family got really upset especially my husband. Now I occasionally take the ‘normal’ host as it is embarrassing to stick out in a crowd and I dislike having people speaking about me.” (Female, 55 years; diagnosed 18 years ago)

Another non-compliant group may be made up of those individuals who occasionally eat food with gluten and yet experience no discomforting symptoms. These persons try to make sense of these particular episodes and will often describe themselves as ‘being a special type of coeliac’ or ‘one who is outgrowing this condition’. These persons perceive a discrepancy in what the health professionals emphasize i.e.: the need to adhere to the diet and their own experiences i.e.: having no symptoms normally associated with the condition. Moreover individuals often use the presence of symptoms as an indicator of illness and to determine whether a treatment is effective or not.

**Practice points**

1. One must appreciate that patients are active participants in a health care process and that the former will formulate their own beliefs about their illness.
2. The health perceptions of each individual are unique and are built up from a variety of sources. Any problems arising from managing a chronic condition will be confronted on the basis of these health representations.
3. Persons with chronic disease may hold beliefs regarding their treatment which may be in conflict with that of the health professional. These perceptions and concerns must be elicited in order to enhance a therapeutic process.
4. Health professionals when introducing interventions should be sensitive and responsive to the needs and beliefs of the individual with a chronic condition.

**Conclusion**

The reasons for non-adherence to a dietary regimen are diverse. In this article we examined non-adherence from a socio-cognitive perspective. We used a qualitative approach to illustrate not only the illness representation model but to illustrate that patients do use such representation when they describe and think about their illness. Additionally, one should appreciate that there are other possible reasons for non-adherence such as economic, cultural influences as well as difficulties in communication between the health professional and patient. Hence, it is vital for health professionals to appreciate that persons with chronic conditions are active agents in their treatment process and thus, are constantly striving to make sense of an illness experience. Thus, attention should be paid to perceived causes of non-adherence and these issues should be discussed with the patient. Since the clinician and patient may often have different illness representations, discussions between the professional-patient dyad may lead to a greater appreciation and understanding of each others perspective. With the establishment of such a dialogue various confusions and mis-interpretations may be minimized and the health encounter between the patient and health professional may prove to be more satisfying. A number of techniques and procedures for intervention are suggested by Ferguson et al.

**References**

In-crease comfort

Nothing beats Canesten HC 30g for treating a whole spectrum of inflamed fungal infections. Whether you’re treating sweat rash (candidal intertrigo), jock itch (tinea cruris) or athlete’s foot, the triple action formula provides rapid relief. Containing 1% hydrocortisone and 1% clotrimazole, Canesten HC 30g helps wipe out the cause whilst soothing the symptoms. So prescribe the name you trust, and stop the misery of fungal infections.

1% hydrocortisone and 1% clotrimazole

Canesten® HC
Anti-Fungal. Anti-Bacterial.* Anti-Inflammatory

*exhibits activity against Trichomonas, staphylococci, streptococci and Staphylococci
Gastro-Oesophageal Reflux Disease – GORD

Valerie Vella BPharm(Hons), MSc(Clin Pharm)(Aberdeen), MRPharmS

Senior Clinical Pharmacist, St Luke’s Hospital, Guardamangia, Malta
Email: valerie.vella@gov.mt

Key words: gastro-oesophageal reflux, antacids, proton pump inhibitors, H$_2$-receptor antagonists

Symptoms of gastro-oesophageal reflux disease (GORD) have a substantial impact on patients’ everyday lives. In the majority of situations patients can be managed empirically with over-the-counter preparations, however some patients presenting with alarm signs will require urgent referral for endoscopic studies.

Introduction
GORD is a collective term embracing all diseases caused by gastro-oesophageal reflux. Gastro-oesophageal reflux is a disorder in which the oesophageal mucosa is damaged by the reflux of gastric or intestinal contents into the oesophagus and results in patient complaints of heartburn and other symptoms such as ‘burping up’ stomach contents or the taste of bitter contents in the mouth. Although the classical symptom is “heartburn”, at times it presents itself as pain in the centre of the chest, which might mimic cardiac angina or asthma. Twenty-five percent of adults experience heartburn at least once a month and most of these are treated empirically. The prevalence and incidence of GORD has doubled in a period of ten years, and this increase is being linked to dietary and lifestyle changes.

Pathophysiology of GORD
The development of GORD is associated with a disruption of the balance between defensive mechanisms (lower oesophageal closure and oesophageal peristalsis) and aggressive factors (e.g. acid, pepsin, bile salts).

There are three pathophysiologic mechanisms, which predispose a patient to reflux:
1. a spontaneous transient or sustained relaxation of the lower oesophageal sphincter (LOS);
2. a low resting lower oesophageal pressure;
3. increased gastric pressure.

GORD is associated with long-term morbidity and mortality. Complications of GORD are oesophagitis which if severe can cause erosive changes, oesophageal ulcers, strictures, haemorrhage, perforation, aspiration and the development of Barrett’s oesophagus. Barrett’s oesophagus predisposes the patient to the development of oesophageal cancer.

Treatment
The primary aim of treatment is complete clinical remission and prevention of long-term complications. Pharmacists are in an ideal position to monitor, advise and refer patients accordingly.

Lifestyle changes
Some foods are known to irritate the gastric mucosa such as spicy food and citric juices; others may stimulate acid secretion as cola and beer, whereas some are known to lower oesophageal sphincter pressure such as foods with a high-fat content. Although epidemiological studies fail to show any association between food and GORD, some patients may benefit from avoiding such foods. Some drug therapy such as alcohol, beta-adrenoceptor agonists, diazepam, progesterone, theophylline and verapamil, can also exacerbate GORD. Obesity and tight clothes may exacerbate reflux by continuously increasing the gastro-oesophageal pressure gradient.

Additional advice which may benefit patients with reflux symptoms include, smoking cessation, avoiding meals 2-3 hours before lying down and avoiding bending down.

Drug therapy
When recommending drug therapy, pharmacists need to keep in mind patient co-morbidities especially in the elderly and also interactions with other medications.

Antacids can provide relief of mild to moderate symptoms associated with GORD because of their ability to neutralise gastric acid and to increase LOS pressure. However antacids have no role in promoting healing of oesophagitis and consequently are only useful in providing symptomatic relief. Antacids should be used only as an adjunct. Calcium containing antacids should be avoided as they can induce rebound acid section.

H$_2$-Receptor antagonists (H$_2$RAs) can be effective for management of mild to moderate GORD when used in full doses. Healing rates in patients with
mild pre-treatment oesophageal reflux are significantly better than in those with moderate or severe pre-treatment disease. H₂-antagonists should be administered in daily divided doses because gastric acid suppression or neutralization throughout the day is important in the treatment of reflux disease.²

**Proton Pump Inhibitors (PPIs)** inhibit gastric acid secretion for a sustained period of time and are highly effective in the treatment of GORD.² In a direct comparison PPIs were found to be more effective than H₂RAs in relieving heartburn in patients with GORD.³ The disadvantages of PPIs are their relatively slow onset of action, limited activity to the post-prandial period and limited efficacy in reducing nocturnal acid secretion.⁴

**Sucralfate** appears to be effective in resolving mild cases of oesophagitis but it appears less effective in management of severe disease. This drug should be administered four times daily preferably as a suspension because the drug needs to be in direct contact with the damaged mucosa.⁵,⁶

**Metoclopramide** stimulates the motility of the upper gastrointestinal tract without affecting gastric acid secretion. When administered as 10mg four times a day, 30-60 minutes before meals and at bedtimes, it increases gastric peristalsis, which leads to accelerated gastric emptying thus decreasing the intestinal transit. Because of its adverse effect profile and the general lack of gastrointestinal motility dysfunction in adult patients with GORD, its usefulness is significantly limited.⁷,⁸

**Nocturnal reflux**

Patients complaining of night-time GORD should be given particular attention.⁹ Nocturnal reflux designates a greater risk of erosive oesophagitis and additionally these patients have a reduced quality of life as GORD interferes with sleep and consequentially next-day mental and physical functioning.¹⁰ These patients usually benefit from:⁹
- elevating the head of the bed;
- adjusting sleeping position;
- full dose PPI at night;
- low dose PPI on a twice daily regimen; or
- full dose PPI in the morning plus a short intermittent course of an H₂RA at night.

**When to refer patients**

Patients should always be referred for endoscopy studies if they show any of the following:
- ALARM signs;⁶,¹¹,¹²
- GI bleeding (such as haematemesis, melaena)
- Dysphagia
- Unintentional weight loss
- Abdominal swelling
- Epigastric mass
- Persisting vomiting

**Gastro-oesophageal reflux in infants**

Gastro-oesophageal reflux and GORD are common in the first months of life and is often linked to the immaturity of the oesophagus and stomach and the higher liquid intake of infants.¹³ Some also claim that genetic factors are involved.¹³

**Symptoms include regurgitation but occasionally treatment with alginates and PPIs is necessary.**¹⁴ The alginate suspension is licensed only for children over the age of two but the alginate oral powder can be used in neonates unless they are preterm.⁷ The only PPI licensed for use in children (over the age of one year) is omeprazole, which is conveniently available in dispersible tablets.¹⁵ Infants with suspected reflux should always be referred.

**Pregnancy-associated reflux**

It is estimated that 30-50% of all pregnant women experience dyspepsia which is most commonly due to gastro-oesophageal reflux, caused by transient relaxation of the lower oesophageal sphincter. Altered oesophageal motility and increased abdominal pressure may also play a role in the pathogenesis of reflux. Symptoms can occur at any time during pregnancy but are more common and severe during the last trimester.¹⁶

**First-line treatment – Lifestyle advice:**¹⁶
- Avoid precipitating factors as coffee, fatty foods, alcohol, smoking, spicy foods, citrus products;
- Eat smaller meals;
- Do not eat within 3 hours of bedtime;
- Wear looser clothes;
- Raise head of bed when sleeping.

**Second-line treatment – antacids:**

When choosing an antacid for a pregnant patient one must bear in mind that not all antacid preparations are licensed for use in pregnancy. Additionally one must remember to choose a low sodium product especially in patients with gestational hypertension and pre-eclampsia.¹⁶ Patients should also be advised to leave a minimum of 2 hours between antacids and iron supplements.⁷ Licensed antacids include:
- **Co-magaldrox** (magnesium hydroxide 195mg & dried aluminium hydroxide 220mg/5ml) low sodium. Dose: 10-20ml, 20-60 minutes after food and at bed-time, or when required. Manufacturer advises to avoid in the first trimester, as there is no clinical data on exposed pregnancies.¹⁷
- **Sodium alginate** 500mg/5ml (sugar-free) Dose: 5-10ml, after meals and at bed-time when required. Studies have failed to show any significant adverse effects of this product on the course of pregnancy or on the health of the foetus.¹⁸

**Third-line treatment**

None of the H₂-receptor antagonists currently on the market are licensed for use in pregnancy. Cimetidine showed inhibition of testicular descend and genital differentiation in pregnant rodents.¹⁹ Ranitidine crosses the placenta and should only be used during pregnancy if considered essential. Surveillance studies do not suggest that ranitidine presents a major teratogenic risk when used in recommended doses but regardless of this it is still unlicensed in pregnancy.²⁰

Omeprazole is now licensed in pregnancy as there is no evidence of adverse effects on pregnancy or on the health of the foetus at a dose of 20mg once daily.²¹ Other proton pump inhibitors are not recommended, as there is insufficient evidence to recommend the use of these drugs in pregnancy.²²

Patients should be referred if:
- symptoms do not respond adequately to lifestyle measures and over-the-counter preparations;
- they are not eating sufficiently or are progressively loosing weight;
- they have signs and symptoms of GI bleeding, dysphagia or persisting vomiting.¹⁶
Conclusion

Despite major advances in the understanding of GORD, management remains a challenge, as some patient needs are still unmet.\(^3,7\) New products, which have a faster onset of action, complete acid inhibition together with improved duration of efficacy, are being developed. These include potassium competitive ATPase blockers (PCABs), histamine H\(_2\) agonists and gastrin antagonists.\(^8\)

References


Practice points

• Gastroesophageal reflux is a lifelong disease that requires lifestyle modifications as well as medical intervention.
• Self-treatment with antacids or alginate therapy may be appropriate for immediate relief of occasional heartburn, however their duration of action is less than two hours.
• Magnesium containing antacids should not be used in patients with renal failure.
• H\(_2\) RAs have a delay in onset of at least 30 minutes however they provide heartburn relief for up to 8 hours. Recommend to take preparations before meals known to cause heartburn.
• Proton pump inhibitors are increasingly being used first line as they provide superior efficacy and once-daily dosing regimen.

Social

The Malta College of Pharmacy Practice would like to congratulate the following leading members of the profession who have recently obtained a Masters degree in Business Administration from Henley Management College, UK.

• Mr Hilary Paul Agius, BPharm, MBA (Henley), currently General Manager (Pharma), GlaxoSmithKline (Malta).
• Mr Josef N. Grech BPharm(Hons), MSc(Syd), MBA (Henley), MRSC, MIM (Hon), currently Group Chief Executive Officer with a local group of companies with various business interests.
• Ms Josette Sciberras, BPharm(Hons), MBA (Henley), currently Head of Pharmacy Department, St Lukes’ and Mater Dei Hospitals.

We would also like to congratulate:

• Ms Louise Azzopardi BPharm(Hons), MPhil(Glasg), Senior Clinical Pharmacist at St Lukes’ and Mater Dei Hospitals for obtaining a Masters degree from the University of Stratchclyde.
• Ms Ruth Theuma BPharm(Hons), MSc(Clin Pharm)(Aberdeen), Senior Clinical Pharmacist at St Lukes’ and Mater Dei Hospitals and MCPP Secretary for obtaining a Masters degree in Clinical Pharmacy from Robert Gordon University, Aberdeen.

We would like to take this opportunity to welcome all the final year pharmacy students into the profession and wish them a successful career. We look forward to having them become members of the College and participating in both educational and social events.
Medicines: mere generic facts

Vanessa Bugeja BPharm (Hons), PQ Dip (Nutrition & Dietetics)

Pharmacist, National Medicines Policy & Audit Unit, Health Division, Malta
Email: vanessa.a.magro@gov.mt

Key words: innovative medicine, generic name, proprietary name, substitution

Originator and generic medicines are often identified either by their generic name or their brand name. Good Manufacturing Practice (GMP) standards ensure that medicines are of high quality, and thus support policies of generic prescribing and generic substitution. The substitution model adopted in Malta promotes rational use and favours competition between different brands. Competition is essential for inducing innovation of medicines and for the sustainability of the pharmaceutical industry. The availability of medicines, the knowledge on these medicines and confidence in their use, are crucial for the rational use of medicines as well as for the strengthening of the medicines market.

Introduction

All medicines which are placed on the market have at least three names. The chemical name is based on its chemical structure. The generic name also known as international non-proprietary name (INN), reflects the active ingredient and the proprietary name is usually a registered trademark.1,2

An original medicinal product has a unique trade name for marketing purposes, also known as the brand name.4 On the market, one finds branded generics or unbranded generics. The branded generics also have a specific trade name, while the unbranded generics use the INN and the manufacturer’s name. Generic names indicate the medical class thus providing the health care professionals with the drug’s pharmacology and classification. Generic names are international. Brand names for the same drug may vary between countries.2,3

Some doctors may be reluctant to prescribe the generic name while patients may not accept a different brand name than the usual.1 The knowledge or lack of it, may be determining the attitude and behaviour of both health professionals and patients towards medicines, and this reflects on the rational or irrational use of medicines.

Originator and generic medicines

The originator medicinal product is the first version of a pharmaceutical, developed and patented by an originator pharmaceutical company which has exclusive rights to marketing the product in the European Union (EU) for 15 years.2

A generic medicine is a pharmaceutical product which is no longer protected by a patent and thus can be copied by other pharmaceutical companies and marketed either under its own brand or as an unbranded product, ideally at a cheaper price. These manufacturers do not face the risks and costs linked to the research and development (R&D) of innovative, originator medicines. The pre-clinical tests and clinical trials are not necessary. Instead, bioequivalence studies are carried out.4 Thus, a company which decides to formulate and manufacture a generic medicine, has to ensure that it is bioequivalent to the original trade-name drug, and that appropriate active ingredients are used, and that it is manufactured according to Good Manufacturing Practice (GMP) standards.5,6 Bioequivalence implies that two medicines are pharmaceutically equivalent and their bioavailability is similar to such a degree that their effect can be expected to be essentially the same.1 The inactive ingredients used may be different and may, though rarely, cause unusual reactions in the body.5

Since the accession of Malta in the EU in May of 2004, the EU legislation with respect to medicinal products, their manufacture and supply, has been adopted. The transposition of the EU legislation into the national legislation – Medicines Act, 2003 and its subsidiary legislation – has provided a legal framework which ensures that both originator and generic medicines available in Malta, meet specific standards of quality, safety and efficacy.1,7

This legislation deters medicinal products of dubious quality from reaching the market and boosts the confidence of healthcare professionals and patients in using any of the medicines available.

Prescribing of medicines

The discovery and development of new medicines is very costly. During the patented period, an innovator medicine is granted monopoly so that this period could possibly be one of high expense to the health service provider or the patient. In this period, the product is marketed extensively and by the time the patent expires the brand name is strongly associated with the generic name in many prescribers’ minds.1

Active, continuous encouragement and promotion of generic prescribing has been shown to increase the rate of generic prescribing, which in turn promotes competition and exerts a downward pressure on the prices of medicines.4 The prescription process could be an essential source of efficiency within a health care system.10 In Malta, doctors are trained to prescribe by generic name, and in the Government Health Services, a ‘generic prescribing policy’ is
in place. The procurement of medicines by the Government Pharmaceutical Services, is based on the generic name of the medicine. Generic prescribing facilitates substitution when a medicinal product with a different brand name is made available.

Both the patient’s therapeutic needs and the financial situation determine what medicines a doctor prescribes. Generic prescribing may be limited by the belief that generic medicines are of poorer quality than their originator counterpart. Two preparations formulated by two different manufacturers cannot be exactly identical.1 However, regulations regarding standards of manufacture and Marketing Authorisation ensure that they are bioequivalent and meet requirements of quality, safety and efficacy.2,6 If an originator branded product is more expensive than the generic alternative, it does not mean that the originator brand is of superior quality or efficacy, and vice-versa.3

Substitution of medicines

The EU aims to make efficacious, high quality and safe medicines readily accessible to patients. Amongst its objectives, one finds the promotion of clinical and cost-effective prescribing and of the wider and appropriate use of generic medicines.11

Generic substitution is the practice of substituting a pharmaceutical, whether marketed under a trade name or generic name (branded or unbranded generic), by a pharmaceutical, often a cheaper one, containing the same active ingredient(s).4 However, different policies and different models are adopted by the EU Member states.5 One model allows the replacement by the pharmacist of the prescribed branded drug by a generic with the same active ingredient, possibly without consulting either the patient or the doctor. Some argue that doctors should be able to prescribe branded medicines as they know what is best for the patient. Substitution may induce the prioritization of economic considerations over patients needs, and a model which supports the substitution of originator brand with the generic medicine might give generics an unfair competitive advantage.4,11

The generics substitution should promote the rational use of medicines so that patients receive medications appropriate to their clinical needs (Table 1), in doses that meet their individual requirements, for an adequate period of time, and at the lowest cost to them and their community.12

The model of medicines substitution adopted in Malta supports the rational use of medicines. In fact according to the current legislation, “Upon presentation of a prescription for a medicinal product, unless the prescriber specifically requests a particular branded product by writing “branded” or “®” on the prescription, a pharmacist can dispense the medicinal product prescribed or an equivalent medicinal product having the same chemical entity, dose, dosage form, formulation and dosage frequency as the medicinal product indicated on the prescription.” (Article 80, Medicines Act, 2003).7

Thus, in Malta the prescriber can prescribe a particular branded product where it is deemed necessary. On the other hand, the pharmacist may substitute the prescribed medicine with a less expensive alternative, which could be either the originator or a generic medicine. This model provides several advantages to pharmacists, doctors and patients. Community pharmacists do not need to stock several different brands of the same medicine as the pharmacist has a choice over which brand may be dispensed. Thus, wastage of money and expired medicines is less likely. A pharmacist may buy one brand in bulk thus ensuring that the generic drug is always available for the patients. A delay in the start of treatment and inconvenience to the patients are avoided when a generic equivalent to the prescribed medicine is available.7 Those patients who cannot afford certain branded medicinal products can be offered an alternative which aids in lowering their financial burden.

Similarly to other policies which promote rational use, generic substitution can be quite controversial and thus may encounter opposition.13 Doctors and pharmacists could have a financial interest in prescribing or dispensing those medicines with the highest profit margins. Doctors may see generic substitution as an interference with their freedom to prescribe. The prescribing and dispensing of newly marketed or expensive medicines could be associated with a certain status.15 Inappropriate promotion and lack of information for health professionals and consumers can result in misunderstandings which in turn lead to irrational use of medicines.

In Malta, besides the legislation governing the substitution of medicines, there are also the Advertising Regulations which govern the promotion of medicines.14 These regulations help to decrease the influences which misleading claims and financial incentives may have on the rational prescribing, dispensing and use of medicines. Information on the medicines authorized and marketed in Malta is provided by the Malta Medicines List published on the website of the National Medicines Policy & Audit Unit (NMPAU) within the Ministry for Health, the Elderly and Community Care (MHEC).15 This list is classified by the Anatomic Therapeutic Chemical (ATC) code and enables the identification of alternatives available.

Medicines expenditure

The key objectives of a government’s medicines policy should include the identification of medicines that bring the greatest benefit to patients, ensuring early access to medicines and providing choice of high value medicines.16 Affordable prices are an important prerequisite for ensuring access to good quality essential medicines.11,17 Affordability depends on pricing policies, price negotiations and

<table>
<thead>
<tr>
<th>Table 1. Situations where generic substitution may not be appropriate2,3,8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The medicine has a narrow therapeutic window e.g. digoxin, warfarin</td>
</tr>
<tr>
<td>2. Plasma levels have to be measured and the dose of the medicine has to be carefully titrated against clinical effect</td>
</tr>
<tr>
<td>3. The pharmaceutical preparation is a modified-release preparation</td>
</tr>
<tr>
<td>4. The inhalers are CFC free</td>
</tr>
<tr>
<td>5. The preparation has many active ingredients</td>
</tr>
<tr>
<td>6. The patient suffers from an intolerance to an excipient</td>
</tr>
<tr>
<td>7. There is an issue of patient compliance</td>
</tr>
<tr>
<td>8. Patient may not be reassured and will not accept a substitute to the usual brand</td>
</tr>
</tbody>
</table>

Issue 13 Summer 2007

Journal of the Malta College of Pharmacy Practice
the promotion of competition. A study which analysed the policy environment surrounding the retail market of generic medicines in 11 European Union countries concluded that if the 10 most commonly prescribed and used medicines were replaced by generic medicines, government spending on medicines could be reduced by between 27% and 48%. In the EU, the rate of spending on medicines is growing faster than the economies and thus the promotion of the use of cheaper alternatives would help governments contain drug expenditure. Cheaper alternatives are a result of the price competition induced by safe, effective, high quality generic medicines. The latter also provide an incentive for the development of innovative medicines and a reduction in the prices of the originator brands.

Products which are still patented are affected by price competition, as most often the drug whose patent has expired would be a therapeutic alternative for still patented drugs. Thus, the effects of generic substitution are not limited to the generics market. It also affects the competition in an entire therapeutic area. Generic substitution can thus reach its full benefits within an efficient marketplace where there is free competition.

The uptake of generics can be stimulated effectively by efficient and fast regulatory procedures, legislation, generic substitution, information campaigns, reference-pricing systems, reimbursement systems and prescribing budgets. These same instruments must be also effective in stimulating competition between different brands, so as to ensure long-term sustainability of the medicines industry. The latter also depends on the creation of an environment that encourages pharmaceutical innovation and fosters the research-based development of new and better medicines.

References


Practice points

1. Medicines have three names: chemical name, generic name and brand name.
2. In the ATC classification system pharmaceuticals are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.
3. In Malta, substitution of a medicinal product with an equivalent alternative can be done.
4. As increasing demands are being made on healthcare services, generic medicines provide a major benefit to society by ensuring patient access to quality, safe and effective medicines.
5. Any medicines policy must take into account the need to have an environment which supports the research and development of innovative medicines, which are essential for patients as well as for the sustainability and general equilibrium of the medicines market.
L.N. 292 of 2006

MEDICINES ACT
(CAP. 458)

Prescription and Dispensing Requirements Rules, 2006

In exercise of the powers conferred by Articles 29 (2) and 82 of the Medicines Act, the Licensing Authority has made the following rules:

1. (1) The title of these rules is the Prescription and Dispensing Requirements Rules, 2006.

(2) These rules shall be deemed to have come into force on the 1st December 2006.

2. (1) These rules apply to medicinal products and to products or substances not classified as medicinal products but which have been deemed by the Medicines Authority to require a medicinal prescription for their use.

(2) The provisions of these rules are without prejudice to those stipulated in the Free Medicinals (Prescription Forms) Regulations, 1996 in respect of prescription forms for free medicinals.

3. Every prescription shall:

(a) be easily legible and written in ink or in other indelible manner;

(b) bear the date on which it is written, clearly indicate in a legible manner and in block letters the full name, and contact details, such as the telephone number, of the prescriber as well as the registration number assigned by the relevant council, and shall be signed accordingly in original;

(c) bear the name, age and locality of current residence of the patient and the name, strength, dosage form, quantity and duration of treatment of each prescribed product included in the said prescription, together with clear instructions on how the prescribed product is to be taken or used. Repeat prescriptions are to be marked accordingly indicating the total period of duration of treatment; and

(d) in the case of computer generated prescriptions, bear the details in paragraphs (a), (b) and (c) hereof and be signed in handwriting by the prescriber.

4. (1) It shall not be lawful for any person, not being a pharmacist duly licensed to practise in Malta, to dispense a prescribed product against a prescription.

(2) It shall not be lawful for any pharmacist to dispense any product to which these regulations apply except on a prescription issued from persons duly authorized under article 81 of the Medicines Act, unless the product is deemed by the Licensing Authority not to require a prescription.

(3) Verbal instructions over the telephone shall not be accepted and honored unless the following conditions are satisfied:

(a) that the pharmacist is satisfied that the verbal instruction over the telephone is being requested by a person duly authorized under article 81 of the Medicines Act, who by reason of an emergency is unable to furnish a prescription immediately;

(b) that the prescriber undertakes to furnish the pharmacist with a prescription complying with the provisions of rule 3 hereof within 48 hours of the verbal instructions;

(c) that the product is dispensed in accordance with the directions of the prescriber; and

(d) that an entry is made into any record kept under the Medicines Act:

Provided that these conditions shall not apply to narcotic or psychotropic substances.

(4) It shall not be lawful for any pharmacist to dispense a product against a prescription after the expiry of six months from the date specified in rule 3(b) hereof, unless it is a repeat prescription, in which case it shall only be dispensed other than in accordance with the directions contained in the repeat prescriptions.

(5) If a prescription is more than six months old, the patient shall be referred to the prescriber for reassessment.

(6) In the case of antibiotics, the prescription shall not be dispensed after ten days from the date of issue of the prescription.
5. The dispensing pharmacist shall write clearly and legibly thereon in ink or any other indelible manner the word “dispensed”, date of dispensing, the quantity supplied, the Pharmacy Council registration number, signature and endorse the prescription with the pharmacy stamp.

6. (1) A pharmacist dispensing a prescription shall enter into any record kept under the Medicines Act the following particulars:

   (a) the date on which the prescription is dispensed:

   (b) the name, quantity and the pharmaceutical form and strength of the product:

   (c) the full name of the prescriber and his registration number:

   (d) the date of the prescription: and

   (e) in the case of medicinal products dispensed in compliance with sub-rule (3) of rule 4, the date on which the prescription is received.

   (2) The requirements of sub-rule (1) shall be satisfied in the case of computerized records, provided that the information is also retained in the form of a print-out for each day on which the pharmacy is open. Such print-out shall be dated and certified by the managing pharmacist on the day to which the print-out relates or within a period of 24 hours thereafter.

7. The provisions stipulated in the Dangerous Drugs Ordinance, and in the Medical and Kindred Professions Ordinance, in respect of prescriptions for narcotic and psychotropic substances, shall also apply.
IN OBESE PATIENTS
CARDIOMETABOLIC RISK FACTORS
CAN INCREASE
THE PROBLEM

Acomplia® is the first selective CB₁ blocker and is indicated for use as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m²), or overweight patients (BMI ≥ 27 kg/m²) with associated risk factors such as Type 2 Diabetes or dyslipidaemia.

Obesity has an impact on multiple Cardiometabolic Risk Factors that contribute to the development of Type 2 Diabetes and cardiovascular disease.

Compared with placebo, ACOMPLIA® demonstrates significantly greater reductions in weight and waist circumference.

In addition, compared to placebo, ACOMPLIA® demonstrates significantly greater:
- improvements in glycaemic control (HbA1c)
- increases in HDL-c
- reductions in triglycerides

An estimated 50% of the effects of ACOMPLIA® on Cardiometabolic Risk Factors are beyond those expected from weight loss alone.

It’s not what you lose. It’s what you gain

Further information is available from:
Sanofi - Aventis Malta Ltd.
Trig Il-Kan. Karmenu Pirlo, B’Kara. BKR 1114 - Tel: 2146 3022

References:
1. ACOMPLIA® Summary of Product Characteristics.
3. Data on file.06-771: sanofi-aventis

MT-RM-07-05-05

procking Information
Presentation: Biconvex, bead-shaped, film-coated white tablets containing 20mg rimonabant.
Indications: As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m²), or overweight patients (BMI ≥ 27 kg/m²) with associated risk factors such as Type 2 Diabetes or dyslipidaemia.

Dosage and Administration: 20 mg tablet daily to be taken in the morning before breakfast. Treatment should be introduced with a mildly reduced caloric diet. Safety and efficacy of rimonabant have not been evaluated beyond 2 years. See also Precautions and Warnings below.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, lactation.

Precautions and Warnings: Use with caution in patients over 75 years of age. ACOMPLIA® should be used with caution in patients with moderate hepatic impairment or epilepsy, and is not recommended in patients aged up to 18 years, or patients with severe hepatic impairment or severe renal impairment. Since ACOMPLIA® tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Patients should be instructed not to increase their dose of ACOMPLIA®. Depressive disorders have been reported in patients receiving rimonabant. The ray should not be initiated in patients with uncontrolled serious psychiatric illness such as major depression, until this psychiatric condition is controlled. Use of rimonabant is not recommended in patients taking antidepressant medication. Patients who have had a cardiovascular event less than 6 months ago were included in the studies for rimonabant. Interactions: Rimonabant should be used with caution in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, rifampicin, ritonavir, clarithromycin, saquinavir), which may increase the plasma concentration of rimonabant (CYP3A4 inducers e.g. rifampicin, phenytoin, phenobarbital, carbamazepine). St John’s Wort may reduce the plasma concentration of rimonabant and may result in loss of efficacy. Pregnancy and Lactation: Use in pregnancy is not recommended. Patients should notify their physician if they become pregnant during treatment with rimonabant. Use is contraindicated during lactation. Effects on ability to drive and use machines: Rimonabant is devoid of any significant cognitive or relative effect.

Adverse Reactions: Very common - upper respiratory tract infection and nausea. Common - gastroenteritis, anxiety, insomnia, mood alteration, depressive disorders, irritability, paresthesia, nervousness, sleep disorders, dizziness, memory loss, hypoaesthesia, sciatrica, hot flushes, diarrhoea, vomiting, pruritus, dyspepsia, tinnitus, muscle cramp, muscle spasm, influenza, asthma, fatigue, joint sprain, confusion, fall risk, hallucinations. Please consult SPC for full details of the recognised side effects with ACOMPLIA®.

Overdose: Experience in overdose is limited. Only minor symptoms have been reported such as headache, somnolence, fatigue and insomnia in single dose tolerance studies.

Just One a Day.
Such a convenient choice for your cholesterol patients.

- One Becel pro-activ yoghurt mini drink (100 g) contains 2g of plant sterols. Clinical studies have proven that this is the optimal dose to achieve substantial cholesterol-lowering.¹,²

- Plant sterols block the absorption of cholesterol resulting in dramatic lowering of the LDL-cholesterol level.³,⁴

- For best results consume with a meal, as part of a healthy diet.

In order to reduce cholesterol levels and achieve a healthier heart, World Heart Federation recommend taking regular physical activity and eating a balanced diet rich in fruit and vegetables, low in saturated fats and including foods that contain plant sterols.

To learn more and apply for patient information packs, visit www.becel.de, phone 08000-72 52 35 or send an email to proactivscienceinfo@unilever.com.