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Very rare: jaundice, hepatitis, haematuria, polyneuropathy and memory loss and arthralgia. Other usually transient side effects: elevation in CK levels, proteinuria. Other adverse events listed as unknown: diarrhoea, Stevens-Johnson syndrome, oedema, cough and dyspnoea. The following adverse events have been reported with some statins: depression, sleep disturbances including insomnia and nightmares, sexual dysfunction and exceptional cases of interstitial lung disease, especially with long term therapy. **Legal Category:** POM. **Marketing Authorisation Number (s):** PA 970/57/1-4. **Marketing Authorisation Holder:** AstraZeneca UK Ltd, 600 Capability Lane, Luton, LU1 3LU, UK. Further information is available on request from: AstraZeneca Pharmaceuticals (Ireland) Ltd., College Park House, 20 Nassau Street, Dublin 2 Telephone: (01) 6097100; Updated 06/10 CRESTOR is a trademark of the AstraZeneca group of companies. 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Pharmacy workforce in Malta

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Editor

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Data retrieved from Pharmacy Council's Annual Report makes a very interesting read in terms of pharmacy manpower on the island.¹ The data was gathered through the forms sent to pharmacists for renewal of licence. While not all pharmacists sent in the requested information (25.9%), the data gathered gives a good indication of pharmacists according to areas of practice. By the end of 2010, the number of pharmacists on the EU list i.e. those registered to practice in Malta stood at 925. This may come as somewhat of a surprise to those seeking to employ pharmacists in community pharmacy and in the public sector where the significant shortage of pharmacists is palatable. Shortage within the pharmacy workforce is an international concern and not just restricted to our island. In line with international trends, the profession is still dominated by females both in terms of sheer numbers and leadership positions. The high proportion of females in the profession has significant implications for the workforce, with women choosing to take career breaks – be they short or long- in order to raise a family and will thus be absent from the effective workforce for a period of time.

When looking at pharmacists by area of practice we find that 33.7% of those that declared their area of practice (685) work in community pharmacy on a full time basis. While this implies that just over one third of registered pharmacists work in community, it does not provide a comprehensive picture of those whose principle occupation is in community pharmacy, as a number of pharmacists have a principle occupation in community pharmacy, but only work on a part-time basis. About 9.8% practice in the other traditional area of practice - hospital pharmacy. This contrasts with UK data where 66% practice in community, and 18% practice in NHS hospitals,³ while in the US about 53.8% of pharmacists practice in community pharmacy.²

Following community pharmacy, the area where most pharmacists, 22.9%, practice is in importation and wholesale. This includes pharmacists who work as medical representatives, Responsible Persons and within the regulatory affairs domain of importation and wholesale. This trend is anomalous with the international pharmacy workforce scene. This sector appears to offer an attractive option to pharmacists locally.

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The other main areas of practice are industry (13.4%), Medicines Authority (4.6%). Interestingly, the male to female ratio in the latter areas of practice are about 1:1 as opposed to the community pharmacy where the ratio is 1:1.5 and hospital 1:1.6. When comparing once again with the UK, the percentage of pharmacists in pharmaceutical industry, it's supplier and support agencies industry, is 5.5 %.³

This data implies that the principle employment for the majority of registered pharmacists is in (i) non-traditional areas, (ii) areas that are not directly related to patient care and (iii) areas that do not require a licence to practice. This means that, locally, most of the pharmacy workforce is being drawn away from those

viewed as essential pharmacy services.

A more intensive approach should be taken to study local manpower needs. WHO has long advocated that countries should actively engage in pharmacy manpower development through planning, production (education and training), and management.⁴ The best way forward is through the development of strategic partnerships between stakeholders such as Ministry of Health, Ministry of Education, training institutions, professional bodies, regional and international organisations, amongst others.²

This country therefore needs to make a consolidated effort to study and address manpower issues.

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Evidence-based drug therapy in the management of heart failure

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Educational aims

- To provide an update of the most recent guideline recommendations for the pharmacotherapeutic management of heart failure.
- To distinguish between those drugs which offer symptomatic relief and those which offer prognostic benefit.
- To highlight the monitoring requirements associated with the drugs used.

Key words

heart failure, angiotensin-converting enzyme inhibitors, beta-blockers, loop diuretics, aldosterone antagonists, angiotensin receptor blockers

This article provides an update on the drug treatment for heart failure (HF) mostly based on the recent clinical guidelines issued by the National Institute of Clinical Excellence (NICE).¹ New high quality evidence from randomised controlled trials has resulted in greater value being given to the use of beta-blockers (BBs) and to the use of the hydralazine-nitrate combination. The importance of monitoring laboratory and clinical parameters to ensure safe and effective drug treatment is also highlighted.

Introduction

HF occurs when the heart is unable to deliver blood and oxygen at a rate that meets the requirements of the body. It is characterised by symptoms of breathlessness, fatigue upon exertion, and signs of fluid retention. Some people with HF have left ventricular systolic dysfunction (LVSD), with reduced left ventricular ejection fraction, typically identified on echocardiography. Others have HF with a preserved ejection fraction. Most of the evidence relating to drug treatment is for HF due to LVSD.¹ Two classifications of

the severity of HF are commonly employed (Figure 1). The New York Heart Association (NYHA) functional classification is based on symptoms and exercise capacity and is employed routinely in most randomized clinical trials.² The American College of Cardiology/American Heart Association (ACC/AHA) classification describes HF in stages based on structural changes and symptoms.³

The most common cause of HF is coronary artery disease, which accounts for around 70% of cases.⁴ Other causes are hypertension, valvular disease, and

arrhythmias such as atrial fibrillation. Advancing age, smoking, hyperlipidaemia and diabetes mellitus are among the associated risk factors. Infections, anaemia, alcohol abuse, side effects of medication such as non-steroidal anti-inflammatory drugs, and non-compliance with prescribed treatment can also exacerbate HF.⁵

In Europe, the prevalence of HF is between 2 and 3% and rises sharply at around 75 years of age; the prevalence in seventy to eighty year-old people is between 10 and 20%. In younger age groups HF is more common in men because the most common cause, coronary heart disease, occurs in earlier decades. In the elderly, the prevalence is equal between the sexes.⁵ The overall prevalence of HF is increasing because of ageing of the population, improved survival of patients with coronary artery disease and more effective treatments for HF.⁶

Drug treatment strategy

Patients with HF have a shorter life expectancy and experience symptoms that can reduce their quality of life. The aims of treatment are to reduce the risk of mortality, delay disease progression, control symptoms and improve quality of life.

Over the past two decades, the therapeutic approach to HF patients has undergone considerable change. Several drug classes have been introduced targeting the two biological pathways implicated in progression of the disease, the renin-angiotensin-aldosterone system and the sympathetic nervous system. Current treatment not only concerns symptomatic improvement, but increasingly focuses on delaying disease progression and on reducing mortality.

Angiotensin-converting enzyme inhibitors

There is evidence to support the use of angiotensin-converting enzyme inhibitors (ACEIs) in all patients with LVSD. ACEIs improve symptoms, reduce hospitalisation rate, and improve survival rate.^{7,8,9,10,11} ACEIs should be offered to all patients with HF due to LVSD (Figure 2).¹

ACEIs should be started at a low dose and titrated upwards at short intervals of at least two weeks until the optimal tolerated or target dose is achieved. The safety of treatment with ACEIs is best achieved by monitoring serum potassium, urea, creatinine and estimated glomerular filtration rate (eGFR) before the initiation of ACEIs, one to two weeks following each dose increment, and then every three to six-months thereafter.^{1,5} Hyperkalaemia is

Figure 1: Classification of heart failure by structural abnormality (ACC/AHA), or by symptoms relating to functional capacity (NYHA)

ACC/AHA stages of heart failure		NYHA functional classification	
Stage of heart failure based on structure and damage to heart muscle		Severity based on symptoms and physical activity	
Stage A	At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.	Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
Stage B	Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.	Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Stage C	Symptomatic heart failure associated with underlying structural heart disease.	Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.
Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.	Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

ACC American College of Cardiology; AHA American Heart Association; NYHA New York Heart Association

a potential problem during therapy. Mildly raised potassium levels (5.0-6.0mmol/L) can often be managed by dietary modifications (foods containing high levels of potassium e.g. banana, tomatoes and citrus fruits to be avoided). Cessation of treatment should only be considered if serum potassium is more than 6mmol/L.^{1,5} An increase in creatinine is expected when an ACEI is initiated, but the action taken should be determined by the extent of the rise. According to guidelines from the European Society of Cardiology, an increase in creatinine of up to 50% from baseline or to an absolute concentration of 265µmol/L, whichever is lower, is acceptable. If the creatinine rises above 265µmol/L, but below 310µmol/L, the dose of ACEI should be halved. If the creatinine rises to 310µmol/L or above, the ACEI should be stopped immediately.⁵ According to NICE guidelines, a change in creatinine of less than 30% or in eGFR of less than 25% is acceptable; if the change is greater, the ACEI should be stopped or the dose reduced to a previously tolerated lower dose.¹

Cough is a common adverse effect of ACEIs and switching to an angiotensin receptor blocker is recommended.⁵ Symptomatic hypotension (e.g. dizziness) is also common but often improves with time, and patients should be reassured. Reducing the dose of diuretics and other hypotensive agents should be considered. Asymptomatic hypotension does not require intervention.⁵

Angiotensin receptor blockers

There is significant evidence supporting to use of angiotensin receptor blockers (ARBs) in the management of HF, although this is weaker than that for ACEIs.^{12,13,14,15,16,17} Unlike ACEIs they do not cause dry cough, one of the most common causes of stopping

ACEI therapy. When patients are intolerant of ACEIs, the introduction of ARBs is proposed as an alternative.¹ ARBs are also recommended as second-line treatment if a patient remains symptomatic despite optimal therapy with an ACEI and a BB, especially if the patient has mild to moderate HF (NYHA class II-III) (figure 2).¹ Monitoring of serum potassium, urea, creatinine and eGFR for signs of hyperkalaemia or renal impairment is recommended as for ACEIs.

Beta blockers

Patients who have HF with LVSD should be considered for the introduction of BBs. In these patients BBs have been shown to reduce morbidity, hospitalisation and mortality. BBs of proven efficacy in HF include carvedilol, nebivolol, bisoprolol and metoprolol succinate.^{18,19,20,21,22,23,24}

According to the recent NICE guidelines (figure 2), both ACEIs and BBs licensed for HF should be offered to all patients with HF due to LVSD, using clinical judgement when deciding which drug to start first.¹ This recommendation resulted from evidence from the CIBIS III trial indicating that HF patients derived similar outcome of therapy with ACEIs followed by BBs, to those treated with BBs followed by ACEIs.²⁵ The clinical decision to use one of these two agents before the other depends on the clinical status of the patient. Several factors could affect the choice, including blood pressure, heart rate as well as the presence of symptomatic ischaemia, arrhythmias and other co-morbidities.¹

BBs should not be withheld from older adults and patients with peripheral vascular disease (unless severe), erectile dysfunction, diabetes mellitus, interstitial pulmonary disease and chronic obstructive pulmonary

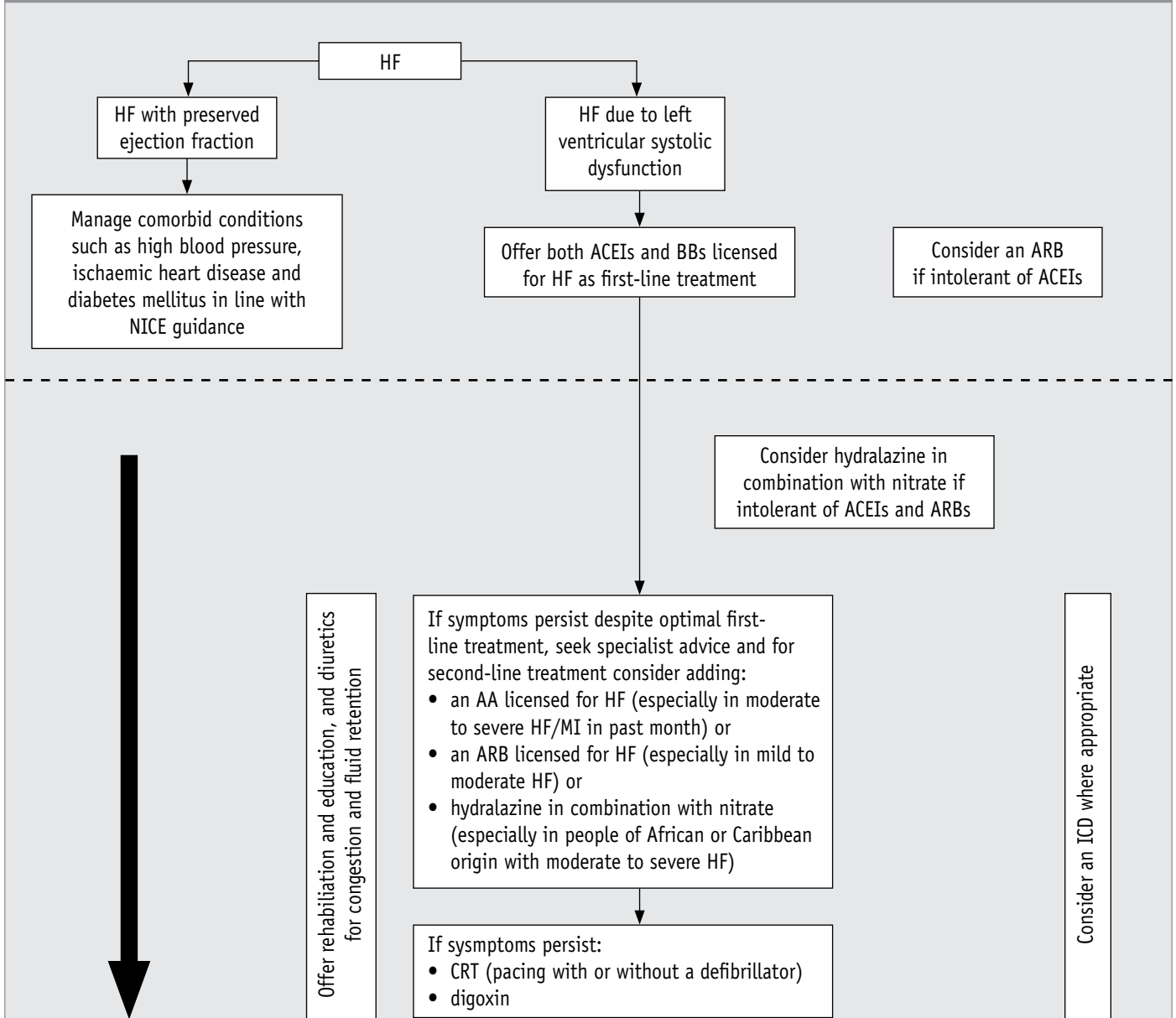
disease without reversibility. Stable patients who are already taking a BB for a concurrent disease (e.g. angina or hypertension) and who develop HF due to LVSD, should be switched to a BB licensed for HF.¹

Treatment should be started in stable patients at low doses and up-titrated slowly at intervals of at least two to four weeks. It is important, during the up-titration of BBs, to monitor the patient's pulse rate, blood pressure and the clinical status, to avoid side effects such as symptomatic bradycardia and symptomatic hypotension. The up-titration should be undertaken gradually and slowly to achieve the target doses used in the clinical trials, if tolerated. The patient needs to be informed that transient pulmonary congestion could occur at times during up-titration of BBs.^{1,5}

Aldosterone antagonists

There is evidence of enhanced activity of the renin-angiotensin-aldosterone system in patients with HF. The modulation of this system started with the introduction of ACEIs, and followed by the introduction of the ARBs in the treatment of HF. Spironolactone, an aldosterone antagonist (AA), was contra-indicated in combination with ACEIs, until the publication of the RALES study in 1999.²⁶ Evidence from this study indicated that moderately to severely symptomatic patients with HF (NYHA class III-IV), despite optimal medical therapy, attained lower hospitalisation rates and higher survival rates with the addition of spironolactone. A more recent trial investigating the newer AA, eplerenone, in patients with LVSD and clinical evidence of HF or diabetes mellitus within 14 days of a myocardial infarction (MI) also showed prognostic benefit in these patients.²⁷ In fact

Figure 2: NICE algorithm for the treatment of heart failure (HF)¹



ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, BB beta-blocker, AA aldosterone antagonist, MI myocardial infarction, ICD implantable cardiovascular defibrillator, CRT cardiac resynchronisation therapy

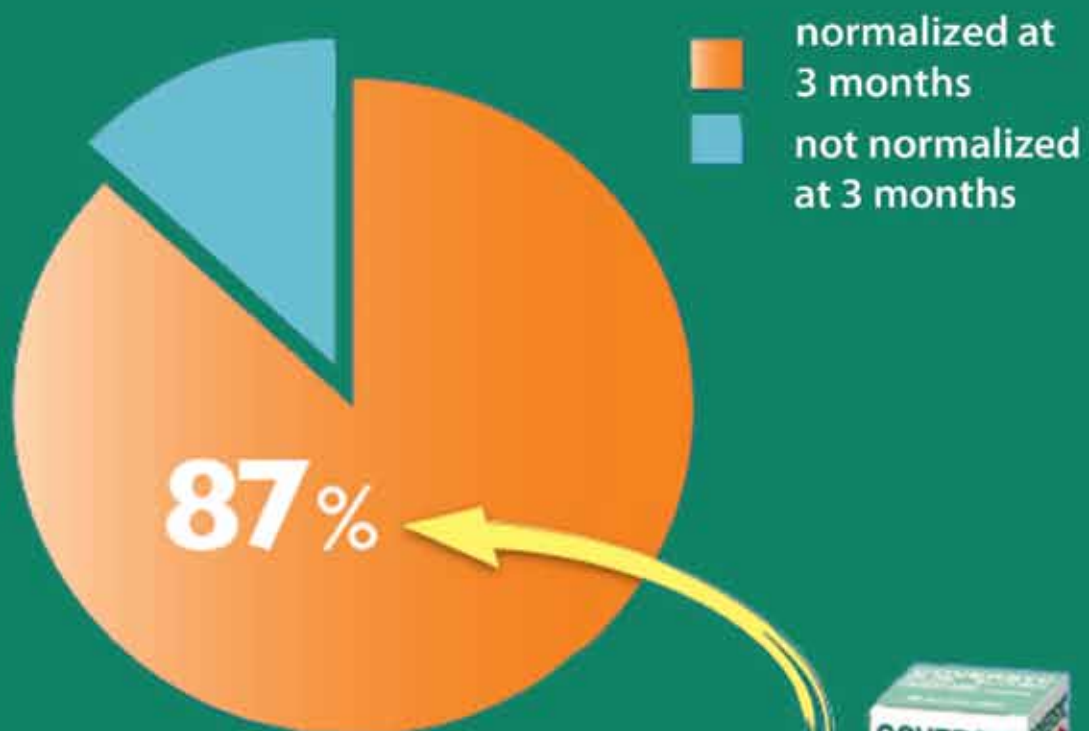
Initial and target doses of selected agents used in the treatment of HF^{5,29}

ACEI	enalapril 2.5mg once daily to 10-20mg twice daily lisinopril 2.5mg once daily to 35mg once daily perindopril arginine 2.5mg once daily to 5mg once daily	hydralazine 25mg three to four times daily to 50-75mg four times daily
ARB	candesartan 4mg once daily to 32mg once daily losartan 12.5mg once daily to 50mg once daily valsartan 40mg twice daily to 160mg twice daily	isosorbide dinitrate 20mg three times daily to 40mg three times daily
BB	carvedilol 3.125mg twice daily to 25-50mg twice daily nebivolol 1.25mg once daily to 10mg once daily	digoxin 62.5-125mcg once daily, up to 250mcg daily in atrial fibrillation
AA	spironolactone 12.5-25mg once daily to 50mg once daily	

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NICE guidelines (Figure 2) recommend that an AA should be considered as second-line treatment if a patient remains symptomatic despite optimal therapy with an ACEI and a BB especially if the patient has moderate to severe HF (NYHA class III–IV) or has had an MI within the past month. For patients who have had an acute MI and who have symptoms and/or signs of HF and LVSD, treatment with an AA licensed for post-MI treatment should be initiated within 3 to 14 days of the MI, preferably after ACEI therapy.¹ From a health economic point of view, the substantially lower cost of spironolactone compared to eplerenone suggests that spironolactone should be used in moderate to severe chronic HF, and eplerenone should be used in the patients with HF following MI.¹

Treatment should be initiated at a low dose and up-titration considered only after four to eight weeks. Hyperkalaemia and a decline in renal function are common among patients prescribed AAs. Monitoring of serum potassium, urea, creatinine and eGFR is recommended at one, two, three and six months and six-monthly thereafter. The dose of AA should be halved if the potassium level rises to 5.5–5.9mmol/L and stopped immediately if potassium is above 6mmol/L. Similarly the dose should be halved if the creatinine level rises to below 220 µmol/L and stopped if creatinine is above 220µmol/L.^{1,5}

Diuretics

The use of diuretics in the treatment of HF is well established and essential for symptomatic relief when fluid overload is present. However, there is no evidence that loop and thiazide diuretics improve the prognosis of patients with HF. Diuretics should be titrated (up and down) according to need following the initiation of subsequent HF therapies. Monitoring of serum sodium, potassium, creatinine and eGFR should be carried out particularly in the acute stage when doses are increased. Care must be taken not to leave patients on unnecessarily high doses of diuretics; the dose should be decreased to the minimum required for symptom control.^{1,5}

Hydralazine plus nitrate

Evidence for the combination of hydralazine and nitrate comes from the AHEFT study in which the addition of the combination to optimal therapy (ACEI, BB and AA) in

Practice points

- ACEIs and ARBs should be started at a low dose and titrated upwards at short intervals of at least two weeks until the optimal tolerated or target dose is achieved. Monitor potassium, urea, creatinine, eGFR and blood pressure.
- BBs should only be initiated or titrated upwards when the patient is clinically stable.
- BBs should be started at a low dose and titrated upwards gradually at intervals of at least two to four weeks until the optimal tolerated or target dose is achieved. Monitor blood pressure, pulse rate and for signs of worsening HF.
- AAs should be started at a low dose and titrated upwards after four to eight weeks until the optimal tolerated or target dose is achieved. Monitor potassium, urea, creatinine and eGFR.
- After an exacerbation, the dose of diuretic should be titrated downwards to the minimal dose necessary to maintain the patient in a fluid-free state. Monitor electrolytes, uric acid, urea, creatinine, eGFR, fluid status and blood pressure.
- Patients on digoxin should be monitored for factors which enhance the risk for toxicity.

black patients with moderate to severe HF (mainly NYHA class III) reduced morbidity and mortality.²⁸ Black patients of African and Caribbean descent have been found to derive less benefit than non-blacks from ACEIs in both HF and hypertension trials, and it is this group to which this evidence is applicable.

NICE guidelines (Figure 2) recommend that hydralazine in combination with nitrate be considered for patients with HF due to LVSD who are intolerant of ACEIs and ARBs. As second-line treatment the combination is to be considered if a patient remains symptomatic despite optimal therapy with an ACEI and a BB, especially if the patient is of African or Caribbean origin and has moderate to severe HF (NYHA class III–IV).¹

Hypotension is a potential adverse effect with this drug combination although it often improves with time. If symptomatic, reducing the doses of other hypotensive agents (except ACEI/ARB/BB/AA) should be considered. Lupus-like syndrome due to the hydralazine component should be considered in the case of symptoms of arthralgia/muscle aches, joint pain or swelling, pericarditis, rash or fever.⁵

Digoxin

Digoxin is one of the oldest known treatments for HF. Although it has an established role as a rate controller in patients with concomitant atrial fibrillation, its indication in HF patients in sinus rhythm is limited. According to NICE guidelines, digoxin is recommended for worsening or severe HF due to LVSD despite first- and second-line treatment for HF (Figure 2).¹

Digoxin is well known for its potential for toxicity. Unwanted effects depend upon the concentration of the cardiac glycoside in the plasma and on the sensitivity of the conducting system or of the myocardium.²⁹ Regular monitoring of plasma digoxin concentration during maintenance treatment is not necessary but is indicated for initiation of treatment, confirmation or exclusion of toxicity, impaired renal function, co-administration of drugs which affect digoxin levels or to confirm patient compliance with the drug.^{5,30} If an assay is indicated, blood should be sampled for digoxin at least six hours after an oral dose is administered. Samples should be taken at least eight days after initiation or change in dose. Sampling times should be recorded if assay results are to be interpreted correctly. The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. Various clinical factors predispose patients to digoxin toxicity. Hypokalaemia, hypercalcaemia and hypomagnesaemia all lead to an increase in responsiveness of cardiac tissues to the effects of digoxin. Correction of these underlying factors is therefore an important part of management.³⁰

Conclusion

Managing HF is a challenge and evidence-based guidelines should be utilised so as to provide optimal treatment and improve patient outcomes. Regular review including monitoring of both laboratory and clinical parameters is essential for safe and effective management.

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Towards the use of safer medicines: why is it important to support the national pharmacovigilance system?

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Educational aims

- To enhance the reader's knowledge on the legal obligations for the reporting of ADRs in Malta
- To have a more thorough understanding of how the Medicines Authority handles ADRs and reports them across the EU pharmacovigilance network.
- To recognise the value of reporting ADRs in the identification of post-authorisation safety signals through established data analysis programmes and analysis techniques
- To be able to appreciate how aggregated pharmacovigilance information is the rationale behind regulatory action on a medicines' marketing authorisation.
- To be informed of the recently published EU directive 2010/84/EC on the community code relating to medicinal products for human use, focusing on the changes that are of interest to healthcare professionals, which are expected to occur with the implementation of this new directive in 2012.

Key words

Pharmacovigilance, Adverse Drug Reactions, Regulatory affairs

All medicinal products carry an inevitable and unpredictable potential for harm that cannot always be detected at the pre-authorisation stage. Pharmacovigilance comprises the science and activities relating to the assessment, understanding and prevention of adverse effects of medicines. The main underlying component of all pharmacovigilance activities is the reporting of Adverse Drug Reactions. With the new directive 2010/84/EC (amending 2001/83/EC) on the community code for medicinal products in the EU it is important that healthcare professionals are refreshed on the need to support pharmacovigilance systems in order to maximise efforts to maintain the safest and most effective medicines on the market.

Introduction

Advances in the process of approval of medicines in Malta and the rest of Europe over the last decade have meant that medicines are approved simultaneously in many countries. In light of the increasing range and potency of medicines, all of which carry an inevitable and sometimes unpredictable potential for harm, supporting the national pharmacovigilance system today is now more important than ever. Pharmacovigilance comprises the science and activities relating to the assessment, understanding and prevention of adverse effects of medicines.¹

The ultimate goal of pharmacovigilance is to contribute to a safer use of medicines. Through this activity:

- Public health is safeguarded, fostering a sense of trust among patients in the medicines they use that extends to confidence in the health service in general.
- Healthcare professionals have evidence-based knowledge on which to base their practise, and so ensuring that risks from medicines use are anticipated and managed.
- Regulators have a solid basis on which regulatory action can be taken.

Mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital.² In practise this means having in place a well-organised pharmacovigilance system³. Pharmacovigilance is an umbrella term used to describe processes for monitoring the safety of medicines. However the main underlying component of all pharmacovigilance activities is the reporting of Adverse Drug Reactions (ADRs).

The Legal basis for Adverse Drug Reaction Reporting in Malta

The Medicines Act of 2003⁴ and subsequent subsidiary legislation, provide the regulatory framework for the Medicines Authority's operations. The Medicines Act as laid out in 2003, required the establishment of a national system for the reporting of ADRs occurring in Malta. In 2006, subsidiary legislation to the Medicines Act, S.L. 458.35 was published under the title "Pharmacovigilance Regulations" stipulating that it is the duty of doctors and other healthcare professionals to immediately report any serious or unexpected adverse reaction to a medicinal product in Malta.⁵ Unexpected ADRs are those ADRs that are

not mentioned in sections 4.4 - 4.9 of the Summary of Product Characteristics (SmPCs). SmPCs and Patient Information Leaflets (PILs) are available online on the medicines authority websites (www.medicinesauthority.gov.mt and www.maltamedicineslist.com).

In December 2010 a new directive by the European Parliament and the Council of the European Union relating to pharmacovigilance was published in the Official Journal of the European Union. This directive (Directive 2010/84/EC) amends directive 2001/83/EC on the community code relating to medicinal products for human use and is applicable to all member states in July 2012.⁶ The introduced legislation will induce changes in the European Union in terms of evaluation of risk associated with medicinal products as well as the framework on how the Union takes harmonised regulatory action on drug safety. The following points are especially relevant to practising healthcare professionals, the pharmaceutical industry and also to patients. The new legislation will bring into force⁷:

- Widening of the legal definition of adverse events to capture medication errors
- Enabling direct patient reporting of suspected Adverse Drug Reactions;
- The inclusion of patients and health-care professionals in the decision-making process.
- The creation of a new European Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) based at the European Medicines Agency (EMA) whose work will focus solely on the assessment and communication of safety issues with medicines. The PRAAC will replace the Pharmacovigilance working party and has the added capability of issuing public hearings which would enhance transparency in decision making. The role of the new committee at the EMA will be to carryout:
 - Evaluation of pharmacovigilance data submitted during all pre- and post-authorisation activities at the EMA and issuing of recommendations
 - Periodic Safety Update Reports (PSURs); evaluation and approval
 - Adverse Drug Reactions signal detection from the EU database of Adverse Drug Reactions, (the Eudravigilance data warehouse) and assessment of identified signals
 - Risk management plans (RMPs) assessment and approval

- Imposition of temporary measures (through the European Commission) to be implemented by Member States to protect patients if the PRAAC considers that a product may not be safe anymore or that a product will not provide any significant therapeutic benefit;
- Assessment of Post-Authorisation Safety Studies (PASS) protocols to be carried out within the Member States as required.
- Further harmonisation with respect to the creation and maintenance of a single frequency date for the submission of Periodic Safety Update Reports (PSURs) by Marketing Authorisation Holders
- Establishing and making public a list of medicinal products for human use under additional monitoring

Medication Errors and Adverse Drug Reactions

As mentioned previously, the definition of the term 'adverse drug reaction' will now be extended to cover not only noxious and unintended effects resulting from the authorised use of a medicinal product at normal doses, but also those arising from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. For the purpose of pharmacovigilance, any medication errors that result in an adverse drug reaction must be reported.

Reporting an Adverse Drug Reaction

The first step in ADR reporting is when a healthcare professional either sends a yellow card (in paper format or electronically) to the Medicines Authority, or directly reports the ADR to the marketing authorisation holder or their local representative. The national ADR form is available at <http://www.medicinesauthority.gov.mt/pub/adr.doc>.

The national ADR form consists of four sections detailing the patient, the adverse reaction, the suspect drug and the reporter. The more information provided, and the more detailed the report the better one can analyse the ADR within a realistic context. Patient details consist of identifiers such as initials, age, gender, weight and height as well as medical history. Information on the medicinal product must be given, ideally both generic and trade names are given, (even for generic medicines, a brand in the form of company name must be given)

as well as dates (even approximate) for starting and stopping the therapy as well as indications for use. The batch number of the product is also very useful information, especially in relation to quality short-falls.

A good description of the adverse drug reaction that is suspected to be related to the medication should follow; describing affected area(s), the severity of the event, the outcome, course of events, and time relationship between therapy and ADR. Information on challenge, dechallenge and rechallenge is also important together with laboratory data if any. Challenging in medicine is when a therapeutic agent is administered in order to observe its outcome. Conversely, dechallenge is when the outcome is observed upon stopping the medicine, and rechallenge is when therapy is restarted after an initial challenge.

The last section details the reporter. This is primarily there to enable reporter and assessor to be in contact in case of the need to follow up a case. It also serves as a means of discouraging fraudulent reporting by individuals. The contact information provided will also be used to send an acknowledgment that the Medicines Authority has received an ADR report.

What happens to reports once they are submitted to the Medicines Authority?

ADR reports may be received by the Medicines Authority either directly from the health care professional (HCP), the public, or indirectly via secondary reporting by the product's Marketing Authorisation Holder. Incoming ADRs are reviewed, evaluated and logged into a database. The receiver analysing the ADR must contextualise the information and if there are any points that require clarification, or more information is required for the analysis of the ADR then the reporter is contacted. The first step of the analysis is checking whether the ADR is expected or not according to the Summary of Product Characteristics. The medicine is then coded by Anatomical and Therapeutic Classification (ATC) and the product's registration status is listed. The next step is checking for the seriousness of each ADR within a safety report against the International Conference for Harmonisation ICH⁸ guidelines for seriousness criteria, since these criteria determine whether a report is transmitted in a normal or expedited way. Expedited reporting is a legal obligation for marketing authorisation holders and competent authorities where any suspected

serious adverse reactions that have been reported to them by healthcare professionals, must be relayed within fifteen calendar days. For a marketing authorisation holder this means that a serious ADR report must reach the Medicines Authority within 15 days, and for the Medicines Authority this means that the report must be given to the European Medicines Agency in 15 days. ADRs are subsequently analysed for a potential biological explanation for the event, taking into account concomitant medications, alternative explanations for the ADR and temporality association.

Distinguishing between the effects of a medicine and the 'normal' course of events within a disease/condition may not always be straight forward. Moreover background incidence of any event is a key consideration and ascribing causality may sometimes prove to be difficult. For example in the case of rofecoxib, a selective COX-2 inhibitor marketed as Vioxx that was withdrawn due to an excess risk for myocardial infarctions (MIs) and strokes. This withdrawal was

based on the results of the clinical trial, 'APPROVe', in patients with intestinal polyps, which had shown an increased risk of confirmed serious thrombotic events (including myocardial infarction and stroke) compared to placebo, following long-term use (over 18 months).⁹ Therefore, in the clinical setting a clear-cut ADR may be one of few, with uncertainty being associated with many reports, especially if the adverse drug reaction at that stage is unknown and unexpected. Uncertainty of whether an event is actually an ADR or not should not be a deterrent from reporting the adverse event.

The minimum criteria for reporting are:

- 1 **a patient with at least one identifier** which may be initials, gender, age, weight, ethnicity, area, the more information that is given the better
- 2 **a medicinal product** name and active ingredient
- 3 **an adverse drug reaction** that is suspected to be related to the drug
- 4 **a contactable reporter.**

The outcome of reporting

The primary incentive for this massive data collection and collation is to extract information on medicines when they are used within the broader clinical context, rather than within the restricted environment of clinical trials. To harmonise and facilitate data collection and collation across the EU, in 2001, the first operating version of EudraVigilance was launched. Eudravigilance is a processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products.

EudraVigilance supports in particular the:

- Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between the European Medicines Agency (EMA), national Competent Authorities, marketing authorisation holders, and sponsors of clinical trials in the EEA;
- Early detection of possible safety signals associated with medicinal products for Human Use;

Table 1: Examples of medicines that have been withdrawn in the last decade

Medicine	Active ingredient	Date of withdrawal	Comments
Propulsid	Cisapride	2000	Withdrawn due to risk of cardiac arrhythmias
Dexatrim	Phenylpropanolamine	2000	Withdrawn due to risk of stroke in women under 50 years of age when taken at high doses for weight loss.
Trovan	Trovafloxacin	2001	Withdrawal due to due risk of unpredictable liver injury
Baycol	Cerivastatin	2001	Withdrawn due to risk of rhabdomyolysis
Vioxx	Rofecoxib	2004	Withdrawn due to risk of myocardial infarction
Distalgesic	Co-proxamol	2004	Withdrawn in the UK due to overdose dangers, will be withdrawn EU wide in end 2011
Melleril	Thioridazine	2005	Withdrawn due to cardiotoxicity
Exubera	Inhaled insulin	2007	Withdrawn voluntarily following restrictions on prescribing, doubts over long term safety
Prexige	Lumiracoxib	2007–2008	Withdrawn due to liver damage
Acomplia	Rimonabant	2008	Withdrawn around the world effected due to risk of severe depression and suicide
Raptiva	Efalizumab	2009	Withdrawn effected due to increased risk of progressive multifocal leukoencephalopathy
Reductil	Sibutramine	2010	Suspended in Europe, due to increased cardiovascular risk
Avandia	Rosiglitazone	2010	Suspended in Europe due to increased risk of heart attacks and death.

- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions;
- Decision making process, based on a broader knowledge of the adverse reaction profile of medicinal products especially in the frame of Risk Management.

Coupled with Eudravigilance is the Eudravigilance Data Analysis System (EVDAS), a programme that statistically analyses the data within the data-warehouse for signal detection. Through this mining of electronic records, the result is generation of signals of specific events that are then investigated, qualitatively and quantitatively through numerous techniques such as Disproportionate Analysis, Proportional Reporting Ratios (PRR), Bayesian Confidence Propagation Neural Networks amongst others. The methodology used by the Medicines Authority within EVDAS is the PRR ratio which is a statistical aid to signal generation developed in the UK. In PRR ratios, the proportion of all reactions to a drug for a particular medical condition of interest are compared to the same proportion for all drugs in the database, in a 2 by 2 table.¹⁰ Additionally, national competent authorities and the EMA evaluate information from supplementary sources such as past and novel medical literature, official company data and international databases to consider the impact on the benefit/risk assessment and thereby allow for proper and timely regulatory action to be taken.

Regulatory safety measures may take the form of the following outcomes:

- Direct Healthcare Professional Communications known as the 'Dear Doctor' Letters where information relating to safety is disseminated across the medical community
- Safety circulars on the medicines authority website which give the latest alerts on medicines
- Media statements by the Medicines Authority when appropriate
- Personal feedback to reporters
- An adjustment to a section/s of the Summary of Product Characteristics which are then submitted as variations to the marketing authorisations
- Urgent safety restrictions, which are interim changes to the product literature, concerning in particular one or more of the following items in the summary of product characteristics: therapeutic

indications, posology, contraindications, warnings, target species and withdrawal periods.¹¹

- Change in Patient information leaflets
- Suspension of a Marketing Authorisation pending further information that alters benefit-risk balance,
- Withdrawal of a Marketing Authorisation

Discussion

Not all hazards can be identified under the limited and restricted environment of testing in clinical trials, before a medicinal product is marketed. Since patients, consumers and healthcare professionals have expectations that medicinal products available are 'safe', they are, from time to time, surprised when regulatory action is taken to restrict their use, introduce new warnings in the product information, or withdraw medicines as a result of the emergence of new data regarding safety issues affecting the positive benefit-risk assessment of the product. Numerous examples can be identified in the literature. Table 1 is a collation of the majority of withdrawals in Europe that occurred in the last decade. In the case of Vioxx in 2004, which was withdrawn due to an increased risk of confirmed serious thrombotic events (including myocardial infarction and stroke), this withdrawal took place after 5 years of extensive marketing. The recent suspension of rosiglitazone, a blockbuster anti-diabetes drug is another example of how a widely prescribed drug showed a degree of toxicity in the post-marketing phase¹⁰. Regulatory action was taken in the EU following a review of new studies questioning the cardiovascular safety of the medicine by the EMA's committee for human medicinal products. Since its first authorisation, rosiglitazone has been recognized to be associated with fluid retention and increased risk of heart failure and its cardiovascular safety has always been kept under close review.

The sibutramine case is another example of why pharmacovigilance is key in the process of maintaining the safest most effective medicines on the market.

Sibutramine gained initial EU approval in 1999. In 2009, preliminary results of a cardiovascular outcomes trial indicated that sibutramine increased the relative risk for major adverse cardiac events by 16% in a population of older over-weight and obese individuals. This outcomes trial (SCOUT) was conducted as a post-marketing

requirement to evaluate the safety of long-term sibutramine, after EU approval of the medicine. The need for this trial came through an accumulation of cardiovascular adverse drug reactions related to sibutramine. Through this trial the EU EMA could conclude that the risk for an adverse cardiovascular event from sibutramine in the population studied outweighed any benefit from the modest weight loss observed with the medicine, and so the marketing authorisation was withdrawn. Pharmacovigilance communications to doctors and pharmacists ensued advising to stop the prescribing and dispensing of sibutramine, while patients taking sibutramine were told to seek alternative weight-loss and weight maintenance programmes.

Conclusion

Proper management and recording of spontaneous ADR reports comprises a critical pharmacovigilance tool useful in identifying unexpected side effects or indicating whether certain adverse effects occur more commonly than previously believed, or whether some patients are more susceptible to ADRs than others. Such findings can lead to changes in the marketing authorisation of the medicine, e.g. restrictions in use, changes in the dose of the medicine and introduction of specific warnings or side effects in the Summary of Product Characteristics. In order to achieve this, the proposed new legislation will strengthen the EudraVigilance database and its data warehouse (the EMA's signal detection software) as the sole EU database. The legislation will also direct National Competent Authorities and MAHs to accept reports sent to them by patients, care givers, families and consumers as well as healthcare professionals. The definition of an adverse drug event will be broadened to also incorporate medication errors. The widening of the definition of an ADR to include and capture adverse events from off-label use and abuse, as well as the introduction of the possibility that the public can also submit ADR reports to the competent authority, is envisaged to strengthen spontaneous reporting systems.

In line with new Pharmaceutical Legislation, a more proactive conduct of Pharmacovigilance will be carried out across Europe, homing onto emerging issues with intensive monitoring in a clinical or academic setting on a large number of

patients. In conclusion it is important to highlight that all medicinal products have benefits as well as risks associated with them. Furthermore not all pharmacological effects of active substances are known, hence vigilant participation of healthcare professionals for new emergent safety issues with long term exposure to medicines is required in order to support the efforts made to maintain safe and effective medicines on the market.

Abbreviations

ADR(s) – Adverse Drug Reactions

MAH(s) - Marketing Authorisation Holders

PRAAC - Pharmacovigilance Risk Assessment Advisory Committee

HCPs – Healthcare professionals

EMA – European Medicines Agency

CHMP – Committee for Human Medicinal Products

SmPC – Summary of Product Characteristics

Key points

- 1 All medicinal products carry an inevitable and unpredictable potential for harm that cannot always be detected at the pre-authorisation stage.
- 2 The main underlying component of all pharmacovigilance activities is the reporting of Adverse Drug Reactions (ADRs) by companies and Health Care Professionals.
- 3 The new pharmacovigilance legislation will widen the legal definition of ADRs, enable patient reporting, increase transparency and enable greater participation by stakeholders.

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Abuse of OTC and prescribed drugs: popping pills for thrills?

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Educational aims

- to understand the various factors which could lead to prescribed and OTC drug abuse.
- to recognize warning signs of prescribed and OTC drug abuse misuse
- to identify best practices in the treatment of prescribed and OTC drug abuse
- to recognize the role of pharmacists in the prevention and education of this key issue in health care.

Key words

prescribed drug abuse, OTC drug abuse, drug misuse, drug addiction

Several studies have shown that there is a high prevalence of prescription and over the counter (OTC) drug misuse among certain population groups. In this paper, an overview will be given as to which classes of groups are mostly abused or misused. An analysis will be given as to the various factors, including associated etiologic and social factors, which could lead to prescribed and OTC drug abuse. Warning signs of prescribed and OTC drug abuse misuse will be described. Best practices in the treatment of prescribed and OTC drug abuse will be given, together with a discussion on the role of pharmacists, health care professionals and regulatory authorities in the prevention and education of this key issue in health care. The benefits of easier access to medicines should be balanced against the potential harm from unsupervised or inappropriate use of prescribed medication.

Introduction

What do Heath Ledger, Anna Nicole Smith, Michael Jackson, Elvis Presley have in common? In all the cases, it was found that the manner of their death was accidental and resulted from the abuse of prescription medications (Table 1)¹. Presley's doctor, Dr. George C. Nichopoulos, had explained the singer's open attitude toward prescription drugs was due to the fact that *"He felt that by getting [pills] from a doctor, he wasn't the common everyday junkie getting something off the street."*²

Is prescribed and OTC drug abuse a modern problem?

Abuse from OTC and prescribed medication is not a new phenomena. The earliest known

records of prescriptions for drugs were found on clay tablets, in 2600 BC ancient Babylon. For many centuries all pharmaceutical products remained totally unregulated and by the 19th century even drugs such as morphine, laudanum and cocaine were readily available through travelling salesmen.³ It was only in 1914 that the US became the first country to introduce legislation which required the sale of drugs, in this case narcotics, to be restricted to licensed physicians or pharmacists.⁴

Why do people abuse drugs?

Various definitions have been used to define drug abuse and misuse. The nonmedical use of prescription or over-the-counter (OTC) medications implies that the user is using

them for reasons other than those indicated in the prescribing literature or on the box label.⁵ The definition several agencies adopt is similar to the US concept i.e:

*Non-medical use, misuse, and abuse of prescription drugs are defined as the use of prescription medications without medical supervision for the intentional purpose of getting high, or for some reason other than what the medication was intended*⁶

Legislation in Europe to regulate the supply of medicines originated 40 years ago following the thalidomide disaster. This led to the European Economic Community Directive 65/65/EEC, which classifies those medicines into classes which require prescription.⁷

What leads to drug abuse and misuse?

Several studies have indicated that patients have a love-hate relationship with prescribed medication. A study carried out on doctors' and patients' perceptions in the decision to prescribe, showed that 40% of patients think illnesses always need drug treatment, 67% patients hope for prescription, while doctors perceive 56% patients wanted prescriptions.⁸

Many of the medications which are abused have legitimate medical uses for people with a variety of illnesses and injuries. They may even be used in high doses for selected medical problems.⁵ Several key factors drive drug abuse. There is a general misperception that abusing medicine is not as dangerous as "street drugs". In addition, there is the added advantage of ease of access of prescribed and OTC medication via medicine cabinets at home, or other person's prescriptions. The internet in recent years has also led to easier accessibility of medicine.⁹ A 2006 survey documented that 89% of internet sites selling controlled prescription drugs in US have no prescription requirements. Of the 11% of sites that required a prescription, 70% only required a prescription be faxed, allowing a customer to easily forge prescriptions or fax the same prescription to several Internet pharmacies. There has also been a trend toward online consultation in lieu of a prescription. In 2006, 99 Web sites offered such a service.¹⁰

It is important to recognise and treat abuse since it can result in decline in work, school, or home performance, legal problems, use in risky situations, and continued use despite social/personal consequences. Dependency can result in tolerance, withdrawal symptoms, decline in normal

activities. The Diagnostic and Statistical Manual of Mental Disorders 4th revision (DSM-IV) definition of drug dependence is not very useful in this context because it relies heavily on the concepts of 'loss of control over the drug' and withdrawal symptoms which are not the main driving force in prescription drug abuse.¹¹

Main classes of drugs of abuse

Trends of increasing abuse of prescription drugs around the world has been reported by the United Nations.¹⁰ Several classes of drugs show up repeatedly in classes of drugs which are abused:

- Opioids and other analgesics e.g. vicodin, oxycontin, tylenol, codeine, dextromethorphan which is found the majority of OTC cough medicines
- Anti-anxiety drugs and Sedative/hypnotics e.g. benzodiazepines
- Stimulants: drugs used for ADHD and weight loss
- Antidepressants
- Image drugs (laxatives, diuretics, steroids)
- Ergogenic aids in sports

Who is most likely to abuse from prescribed/OTC medications?

Several different types of populations are more susceptible to prescription abuse. These include youths, the elderly, pain patients who abuse opiate medications, as well as users with comorbid psychiatric conditions.¹²

Prescription abusing populations: youths

The harmful legal products consumed by youths consist of many different types of substances found in many different products that are readily available to children and adolescents.¹³ Various studies in US have shown that prescribed medication abuse among teens has tripled in the last 10 years. From 1992 to 2003, abuse of controlled prescribed drugs grew at the rate of twice that of marijuana and five times that of cocaine.¹⁴ These studies have shown that an alarming number of teens have a false sense of security about the safety of abusing prescription medications and 40% believe that prescription medicines are "much safer" to use than illegal drugs. 31% believe there's "nothing wrong" with using prescription medicines without a prescription "once in a while" and 29% believe prescription pain relievers are not addictive.¹⁵

Prescription abusing populations: elderly

Although older adults represent 13% of

population, they account for nearly one-third of all medications prescribed and these are prescribed for longer periods than are younger adults. The elderly are associated with multiple medical problems, have a higher incidence of chronic pain thus more possibility of opioid abuse and also can misunderstand directions and this leads to nonadherence. Some elderly patients also have multiple physicians. In addition the problem may be a hidden one since there is denial among family members, peers or care providers.¹⁶

Prescription abusing populations: gender

While men and women have similar rates of use of prescription drugs, gender differences have been observed among girls aged 12-17 years old. Studies have shown that they are more likely to use abusable prescription

drugs, especially opioids and anxiolytics; are two to three times more inclined to be diagnosed with depression and given more psychotherapeutics and twice more prone to be addicted to drugs.¹⁷

Prescription Abusing Populations: pain

Pain is a subjective unpleasant sensory and emotional experience arising from the actual or potential tissue damage or described in terms of such damage. Each individual learns the application of the word through experiences related to injury in early life. There is a complex relationship between drug abuse and use of opioids in pain management, with overlapping vulnerability and psychopathology. It is also associated with the consumption of other substances and inadequate monitoring.¹⁸ Published rates of abuse and/or addiction in chronic pain

Table 1: Drugs found at time of autopsy of Heath Ledger, Anne Nicole Smith, Michael Jackson and Elvis Presley

Name	Drugs found at time of autopsy
Heath Ledger	oxycodone and hydrocodone – diazepam alprazolam temazepam doxylamine
Anna Nicole Smith	chloral hydrate diphenhydramine clonazepam diazepam temazepam oxazepam lorazepam acetaminophen, atropine topiramate ciprofloxacin, (for treatment of abscess on her left buttock from chronic repeated injections of various hormones eg GH)
Michael Jackson	propofol lorazepam midazolam omeprazole, hydrocodone sertraline paroxetine, carisoprodol, hydromorphone
Elvis Presley	as many as 14 different drugs, including codeine and methaqualone Singer had been prescribed between 5,000 and 10,000 tables in the eight-month span before his death.

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populations are approximately 10%. There are in fact several common features between chronic pain and addiction such as early trauma, loss of mastery, loss of control, loss of sense of self, cognitive error.¹⁹

Prescription Abusing Populations: image addiction

Recent years have seen a rise in the misuse of laxatives, diuretics, steroids and diet aids to improve personal appearance. Media promotes "idealistic" body and this can lead to body perception issues. Several are due to a disorder in body image; low self-esteem, depression, suicide and it is more common among career professionals such as models; firefighters; police officers and military personnel. The frequent use of laxatives as a form of weight control can cause serious problems can lead to severe dehydration, heart attack, nervousness hallucinations, high blood pressure, insomnia, confusion, death.²⁰

Prescription abusing populations: drug abuse in sports

Performance-Enhancing Substance are defined as "...any substance taken in nonpharmacologic doses specifically for the purposes of improving sports performance ... by increasing strength, power, speed, or

endurance or by altering body weight or body composition."²¹

Several of these pharmacological agents are drugs used for weight control or enhancement of oxygen carrying capacity, masking agents. They also include anabolic agents, stimulants, peptide hormones. There has been documented increase in misuse of Human Growth Hormone (hGH) especially in US for improving performance in order to ensure sports scholarships.²²

What are the risk factors?

There are four main ways to identify patients at risk: history: personal history & family history; screening instruments; behavioral check lists and therapeutic maneuver and co-morbid psychiatric disorders. Family management problems which could lead to misuse of drugs have been identified by poorly defined rules; lack of monitoring or excessive discipline by parents; negative communication patterns and poor anger management. Absence of healthy recreational or leisure interests, early antisocial behavior (e.g., aggression, hyperactivity, defiance) and academic failure.²³

How to treat misuse and abuse of drugs

Several holistic treatment schemes have been proposed including involvement in

alternative activities; instilling a sense of well being and self-confidence and developing a healthy coping strategies to deal with stress. Patients should have a perspective of "improvement" and the activity should be achievable, enjoyable and meaningful. It is also important to treat educate parents and carers. They should be taught to be observant of over-the-counter drug usage in their adolescent children; the importance of discarding old and unused medications.²⁴

Conclusion

"Determining legitimate medical purpose can be challenging. Despite their best efforts to balance their roles as health care providers and gatekeepers, pharmacists still struggle with the lack of a formal process for dealing with incidents of suspected or recognized abuse."²⁵

Prescription drug abuse is a complex problem, affecting a heterogeneous population and is one which is largely unknown and unaddressed. Pharmacists need to watch for prescription and OTC medication abuse. Adequate prescription monitoring mechanisms lack so pharmacists need to rely on their observation skills and the patient's behaviour pattern over time in order to detect possible prescription or OTC drug misuse.

Possible treatment strategies could include

- inquiring about prescription, OTC, and herbal drug use
- inquiring about drug use
- providing disposal containers that patients can use to dispose of their unused or unneeded prescription or OTC medications;
- careful record keeping of prescription refills.⁵

When deciding if a medicine should be reclassified to make it available over the counter, regulatory authorities must balance the benefits of easier access against the potential harm from unsupervised or inappropriate use. Some countries have an intermediate stage, pharmacy-only sale, where there is still some supervision from healthcare professionals.⁷ Pharmacists should enhance their involvement in health promotion and their understanding safe use of medications and actively develop programs and resources for the benefit of their patients.

Table 2: Commonly Used Prescription Drugs with Potential for Abuse

Category	Drug examples
Sedatives	Barbiturates Flunitrazepam
Dissociative anesthetics	Ketamine
Opioids and morphine derivates	Codeine Fentanyl Morphine Oxycontin Dextromorphan
Stimulants	Amphetamines Cocaine Methamphetamine Methylphenidate
Anabolic steroids	
Tranquilizers and muscle relaxers	Benzodiazepines Carisoprodol
Laxatives	
Diuretics	

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Key points

- Prescription drug abuse is a complex problem, affecting a heterogeneous population and is one which is largely unknown and unaddressed.
 - Many of the medications which are abused have legitimate medical uses for people with a variety of illnesses and injuries.
 - It is important to recognise and treat abuse since it can result in decline in work, school, or home performance, legal problems, use in risky situations, and continued use despite social/personal consequences.
 - Several classes of drugs show up repeatedly in classes of drugs which are abused and several different types of populations are more susceptible to prescription abuse.
 - Parents and carers should be taught to be observant of over-the-counter drug usage in their adolescent children; and the importance of discarding old and unused medications.
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Prevention of cancer through lifestyle change and screening

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Educational aims

- To provide evidence base for prevention
- To describe the lifestyle factors affecting cancer
- To describe effectiveness of screening

Key words

cancer, prevention, lifestyle, screening programmes, effectiveness

Cancer is the leading cause of death worldwide. Evidence shows that about 40% of all cancers are preventable. This article looks at the evidence base for primary prevention measures focusing on lifestyle risk factors of tobacco exposure, overweight and obesity, dietary factors, alcohol and physical activity. Some basic principles of screening and screening programmes are discussed with emphasis on the importance of doing more benefits than harms, at a reasonable cost. We look at the evidence for effectiveness of cancer screening programmes, including randomized controlled trials and touch briefly on the ongoing debates for and against the effectiveness of organized screening programmes. Sufficient evidence exists to demonstrate the effectiveness of screening for breast, colorectal and cervical cancer. Ongoing studies in prostate screening will provide valuable evidence in due course.

Introduction

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008. The number of global cancer deaths is projected to increase by 45% from 2007 to 2030 (from 7.9 million to 11.5 million deaths), influenced in part by an increasing and aging global population. The estimated rise takes into account expected slight declines in death rates for some cancers in high resource countries. New cases of cancer in the same period are estimated to jump from 11.3 million in 2007 to 15.5 million in 2030.¹

The incidence rate of new cases of cancer in Malta is on the increase however the number of deaths from cancer are on a down going trend (Figure 1) especially for some forms of cancer including breast cancer.² This reflects improvements in early detection and treatment.

A recent study has estimated that the number of cancer-related deaths in EU member states for 2011 will be nearly 1.3 million. Using a new mathematical model, the predictions show that cancer mortality rates should fall around 7% for men and 6% for

women compared with 2007.³ Prostate cancer is the most common cancer in males, followed by lung and colorectal. For women breast cancer is the most common followed by lung and colorectal. Lung cancer is the number one cancer killer for both men and women.

There is much evidence which shows that about 40% of all cancer cases are preventable (Table 1). In fact prevention offers the most cost-effective long-term strategy for the control of cancer. Lifestyle factors continue to be causally related to certain cancers including tobacco use, unhealthy diet, alcohol overuse and inadequate physical activity.⁴

Secondary prevention measures include screening. Screening for cancer involves the application of a simple test in a healthy asymptomatic population to identify early disease. The main objective of cancer screening (and subsequent treatment) is to shift the stage at which disease presents thus extending life and reducing cancer mortality. Other important considerations include the economic cost and the potential effects on quality of life, which may be beneficial or harmful. Screening may induce adverse effects, such as over-diagnosis and over-treatment and generation of undue anxiety. Screen detected cases may include indolent lesions, some of which would not progress even if untreated.^{5,6}

Table 1: Preventable Cancers

67% of mouth, pharynx and larynx cancers
75% of cancers of the oesophagus
33% of lung cancers
45% of stomach cancers
41% of pancreatic cancer
16% of gallbladder cancer
43% of bowel cancer
17% of liver cancer
42% of breast cancer
56% of endometrial cancer
20% of prostate cancer
19% of kidney cancer
39% of these 12 cancers combined and
26% of all cancers

Effectiveness of screening is measured in terms of mortality reduction – this is what motivates public health policy makers to implement, manage and evaluate cancer screening programmes.⁷

Primary Prevention Measures

Tobacco

Tobacco is the single largest cause of preventable cancer in the world.⁸ It is responsible for 1.8 million cancer deaths per year and causes 80-90% of all lung cancer deaths, and also causes a number of deaths from cancer of the oral cavity, larynx, oesophagus and stomach.⁹ Tobacco smoke contains about 4000 different chemicals, of which at least 80 of these could cause cancer.¹⁰

Tobacco smoke was first shown to cause lung cancer in 1950 by Doll and Hill.¹¹ Decades of research have consistently established the strong association between tobacco use and cancers of many sites. Specifically, cigarette smoking has been established as a cause of cancers of the lung.⁸ Studies have shown that lung cancer risk is greatest amongst those who smoke the most cigarettes over the longest period of time.¹² Starting smoking at an early age increases the cancer even more than starting later in life.¹³ Tobacco is a major risk factor for several other types of cancer including oral cavity, oesophagus, bladder, kidney, pancreas, stomach, cervix, and acute myelogenous leukemia.^{14,15,16,17} Second-hand

smoke, also known as environmental tobacco smoke, has been proven to cause lung cancer in nonsmoking adults.¹⁸

Smoking avoidance and smoking cessation result in decreased incidence and mortality from cancer. Stopping smoking at 50 years of age would half the excess risk of overall cancer, whilst stopping at 30 years of age would avoid the majority of cancer.¹⁹ The effects of quitting smoking depend on the type of cancer.^{20,21}

Overweight and obesity

Cancer of the colon,²² breast (postmenopausal),²³ endometrium,²⁴ kidney,²⁵ oesophagus,²⁶ are associated with obesity. Some studies have also reported associations of obesity with cancer of the gallbladder, ovaries and the pancreas.²⁷ The risk of postmenopausal breast cancer in obese women is 1.5 times the risk of women of healthy weight.^{28,29} This led to a number of studies related to the risk reduction in persons who were overweight or obese by intentional weight loss. A recent study found that women who experienced intentional weight loss of 20 or more pounds and were not currently overweight, had cancer rates at the level of non overweight women who never lost weight.³⁰ These findings suggest that intentional weight loss might reduce risk of obesity-related cancers. Therefore this adds on the importance that overweight and obese people will gain health benefits by losing weight.

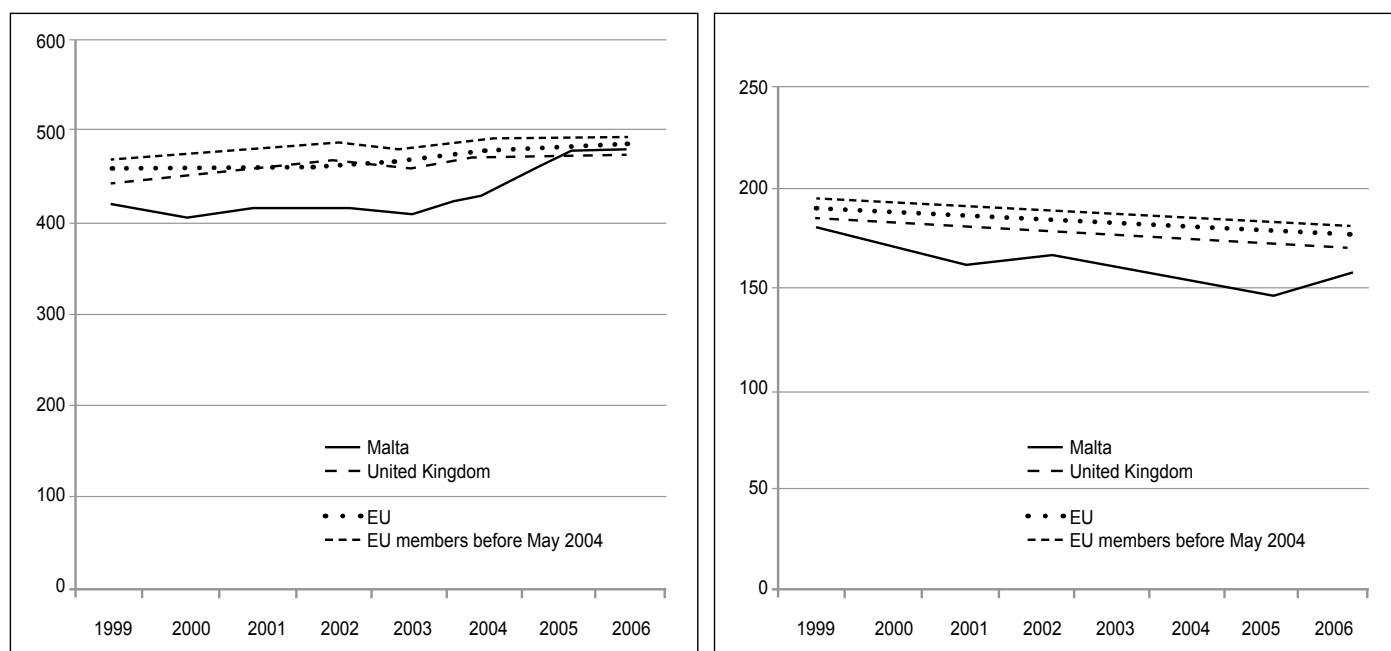
Diet

Apart from the link between overweight and obesity, which is related to diet, there is also some evidence that diet has an effect on cancer. Estimates concerning the potential contribution of diet to the population burden of cancer have varied widely. The exact association between diet and cancer development has not been firmly established. In contrast to the epidemiologic evidence on cigarette smoking and cancer, evidence for the influence of dietary factors and cancer is uncertain. An assessment of the potential role of diet entails measuring the net contribution of diets, comprising factors that may protect against cancer and other factors that may increase cancer risk.

Various reviews,³¹ have shown that the greatest consistency was seen for fruits and non-starchy vegetables. They were associated with “probable decreased risk” for cancers of the mouth, esophagus, and stomach. Fruits, but not non-starchy vegetables, were also found to be associated with “probable decreased risk” of lung and bladder cancer.^{32,33} Vegetables may also have a protective effect against ovarian cancer.³⁴

Literature suggests that eating a variety of foods containing high fiber has a protective effect against colon cancer. Evidence also indicates that a high fiber-containing diet may be protective against breast, ovary, endometrial, and gastrointestinal cancer. However, it is difficult to assess if the protection is clearly

Figure 1: Incidence (left) and mortality rates (right) of Cancer in Malta compared to UK and EU average



from fiber or some other dietary component, such as low fat.³⁵ A randomized controlled trial of supplemental wheat bran fiber did not reduce the risk of subsequent adenomatous polyps in individuals with previously resected polyps. Hence for cancer prevention, the emphasis for dietary recommendation should be on a dietary pattern rather than on an isolated dietary fiber supplement.³⁶

Ecologic, cohort, and case-control studies found an association between fat and red meat intake and colon cancer risk,³⁷ but a randomized controlled trial of a low-fat diet in postmenopausal women showed no reduction in colon cancer.³⁸

Alcohol

Alcohol use is a risk factor for many cancer types including cancer of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and breast. In fact WHO have estimated that harmful alcohol use is responsible for 351 000 cancer deaths per year globally. Risk of cancer increases with the amount of alcohol consumed.³⁹ The risk from heavy drinking for several cancer types (e.g. oral cavity, pharynx, larynx and oesophagus) substantially increases if the person is also a heavy smoker. Attributable fractions vary between men and women for certain types of alcohol-related cancer, mainly because of differences in average levels of consumption. For example, 22% of mouth and oropharynx cancers in men are attributable to alcohol whereas in women the attributable burden drops to 9%. A similar gender difference exists for oesophageal and liver cancers.⁴⁰

Physical activity

A growing body of epidemiologic evidence suggests that people who are more physically active have a lower risk of certain malignancies than those who are more sedentary.⁴¹ It has been established that there is a "probable" association of physical activity with lower risk of postmenopausal breast cancer,⁴² and colon cancer.⁴³ Some evidence also shows a link with lower risk of endometrial⁴⁴ and prostate cancer⁴⁵. As with the dietary factors described above, physical activity seems to play a more prominent role in selected malignancies.

Secondary prevention by screening

"All screening programmes do harm; some also do good. The responsibility of the policy-maker is to decide which programmes do more good than harm at reasonable cost

Key Practice Points

- Many aspects of general health can be improved, and many cancer deaths prevented, if people adopt healthier lifestyles (adopted from European Cancer Code 2003).
- Tobacco should be avoided completely. Assistance is available to help people quit in the form of counselling and group sessions.
- Obesity is a risk factor and needs to be controlled. Physical activity on a daily basis helps prevent weight gain and is directly related to cancer prevention. A healthy diet with vegetables and fruits and decreased consumption of foods containing fats from animal sources are proven beneficial to prevent cancer. Alcohol can only be consumed in moderation.
- Exposure to sun and cancer causing substances should be avoided.
- Public health programmes that could prevent cancers developing or increase the probability that a cancer may be cured include breast, cervical and colorectal screening.
- Vaccination programmes against hepatitis B virus infection can prevent cancers of the liver.

and then introduce them, once they are confident that the screening programme can and will reach the standard of quality required for success."⁴⁶

Appraising the evidence - the effectiveness of screening

A screening programme should have high sensitivity and specificity. Sensitivity is the capacity to detect cases in the pre-clinical detectable phase amongst those screened. Specificity is the ability to correctly identify subjects without the disease. Other measures of performance include screening attendance, reproducibility of screening test, diagnostic procedures used to confirm positive screens and interval between successive screening tests.⁴⁷

A randomized controlled trial (RCT), with mortality as its end-point, is still considered as the optimal and often the only valid means of evaluating the effectiveness of a screening programme. Cohort and case-control studies are often used, and most evidence comes from comparisons of time trends and geographical differences between populations that were subjected to screening of variable intensity. Non-experimental studies do not provide a solid basis for decision making.⁴⁸

The criteria developed by Wilson and Jungner,⁴⁹ have stood the test of time well and are still useful today. There have since been broad debates stimulated by the evidence-based decision making movement and the Cochrane collaboration. In a hierarchy of evidence, a systematic review of randomized controlled trials is usually placed at the top. However, disputes remained unresolved, because value judgments are involved in the selection or rejection of trials

to be included in the systematic review. This was most fiercely argued in the debate about breast cancer screening when a review in *The Lancet* suggested that the evidence for screening was biased by the inclusion of trials of low quality.⁵⁰ An extensive exchange of letters took place until the issue was reviewed by IARC, the International Agency for Research on Cancer, which published a report concluding that: "...trials have provided sufficient evidence for the efficacy of mammography screening of women between 50 and 69 years. The reduction in mortality from breast cancer among women who chose to participate was estimated to be about 35%..."⁵¹

The effectiveness of screening for breast (mammography), colorectal (FOBT) and cervical cancer (Pap smear) have now been firmly established.⁶ Although limitations in the existing evidence base include insufficient evidence about harm and the need to address opportunity costs.⁷

Introduction of the HPV vaccine may reduce the demand for cervical cancer screening by decreasing the risk of disease, but this will take a considerable amount of time to be seen. Screening for prostate cancer has not been fully evaluated but ongoing RCTs should provide important evidence in due course.⁵² Evidence of effectiveness of screening for other cancers remains insufficient or unclear.

Conclusion

Prevention is the key to reducing the burden that cancers have on our health care systems. Regular physical activity and the maintenance of a healthy body weight, along with a healthy diet, and avoidance of tobacco will considerably reduce cancer risk.

Screening is a programme, not a test. Screening programmes mandate a fine and dynamic balance between benefits and harms. Establishing the benefits of screening requires evidence of mortality reduction from large randomized trials, as for breast, and colorectal cancer. In spite of the lack of RCT evidence, screening for cervical cancer with cytological smears has been shown to be effective. Screening tests are available for other cancer types but their efficacy has not been demonstrated effectively. Based on this evidence, Malta launched the National Breast Screening Programme in 2009. The National Cancer Plan 2011-15 announced in February 2011 outlines firm plans for colorectal and cervical screening programmes in the near future. This is complemented by the Non Communicable Disease Strategy launched in April 2010, which outlines the basis upon which programmes are implemented to raise awareness and reduce exposure to cancer risk factors, and to ensure that people are provided with the information and support they need to adopt healthy lifestyles.

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Pharmacogenetics: where do we stand?

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Educational aims

- To emphasize the importance of genetic contributions to observed interpatient variability in drug responses
- To discuss the practical applications of pharmacogenetic/pharmacogenomic knowledge
- To suggest how the introduction of pharmacogenetic tools may require additional skills from health care professionals
- To provide a basic picture of the roles being undertaken by FDA and EMA with respect to pharmacogenetics

Key words

Pharmacogenetics, pharmacogenomics, personalised medicine

“Our drugs do not work on most patients.” Such did Allen Roses, then worldwide vice-president of genetics at GlaxoSmithKline, greet his audience, during a scientific meeting in London in 2003.¹ Nearly a decade has passed since then, and significant strides towards the development of genotype-guided prescribing have been made. Pharmacogenetics and pharmacogenomics are now an established area of pharmacology specialization, and they hold the promise of the key to personalized medicine, leading to safer and more effective patient-focussed therapeutic outcomes.

Introduction

Pharmacogenetics and pharmacogenomics, have often been hailed as the holy grail of therapeutics. Scientists have seen them as a major highway leading to personalized medicine, where the patient’s most personal characteristic, his genetic profile, becomes a fingerprint which can be used to predict the way he will respond to a specific drug. Therapeutic outcome data collected from large clinical trials, may start to lose its meaning, unless those trials are also fortified with pharmacogenomic considerations. *Standardized dosing*, may give way to *genotype-predicted dosing*, perhaps reducing the need for clinically-based individual dose adjustments. Therapeutic drug monitoring data may be combined with genotype data, in order to enhance the maintenance of drug levels within the required therapeutic window. The benefit to risk ratio for most drugs may be improved, with consequently less adverse events, better therapeutic outcomes and improved pharmacoeconomic prospects.

Timeline

Science rapidly makes history. Watson and Crick published their cardinal paper describing the double-helical structure of DNA in 1953.² In 1957, Motulsky suggested that individual differences in drug efficacy and adverse effects might be due to inheritance.³ Two years later, Vogel published his “Moderne problem der humangenetik”⁴ wherein for the first time, the term “pharmacogenetics” was coined and used. This was followed by a landmark paper in 1968, where Vessel and Page showed similar drug pharmacokinetics in identical twins who share 100% of their genes as contrasted to fraternal twins who only share 50%.⁵ This period even preceded the development of DNA sequencing technologies, which started to emerge in the 1970s. Scientific interest in the pharmacogenetic area gradually began to increase, and further landmarks were reported. However, it was only in the mid-1990s that a sudden escalation of peer-reviewed publications occurred, as evidenced by the National Centre for Biotechnology Information (NCBI)-maintained Pubmed database indices. During this period, the US-funded human genome project was underway, and interest in the functional relevance of DNA sequences was increasing in the scientific community. The completion and public availability of the human genome project data in April 2003, ushered us into

Table 1: Some important landmarks in the pharmacogenetics timeline

1953	James D Watson and Francis Crick published their paper on the double-helical structure of DNA. ²
1957	Motulsky proposes that “inheritance might explain many individual differences in the efficacy of drugs and in the occurrence of adverse drug reactions.” ³
1959	The word “pharmacogenetics” appears for the first time in a paper published by Friedrich Vogel. ⁴
1968	Vessel and Page show similar drug pharmacokinetics in identical twins who share 100% of their genes as contrasted to fraternal twins who only share 50%. ⁵
1977	DNA sequencing technologies start to emerge.
1990	The human genome project (HGP) is initiated, and funded by the National Institutes of Health (USA) and other international partners. Projected project timeline is 15 years. ³⁸
2003	The HGP is completed, two years in advance of its original projected target date. ³⁸
2004	Roche AmpliChip Cytochrome P450 Genotyping test is given marketing clearance by FDA. This is the first pharmacogenetic test to be given FDA approval. ²⁶
2005	The European Medicines Agency (then known as EMEA, later known as EMA) establishes the Pharmacogenetics Working Party (PgWP). This later changed its name to the Pharmacogenomics Working Party, still maintaining the PgWP abbreviation. ³²
2005	The Food and Drug Administration (FDA) establishes the Interdisciplinary Pharmacogenomics Review Group (IPRG). ³³
2005	FDA gives marketing approval for The Invader UGT1A1 Molecular Assay. This is the first pharmacogenetic test to be approved by the FDA, following establishment of the IPRG. ²⁸
2009	Imperial College London announce their ongoing development of the SNP Dr pharmacogenotyping device. ³⁷
Today	Major pharmaceutical companies have incorporated pharmacogenomics into the drug discovery process,, published pharmacogenetic data is escalating exponentially, and translation from bench to bedside is well underway.

the post-genomic era. This has brought with it a torrent of new technologies, focussed on global analysis of whole genomes, rather than studies of individual genes. Genetics thus paved the way for genomics, and pharmacogenetics led to pharmacogenomics (Table 1).

What are pharmacogenetics and pharmacogenomics?

The Merck Manual⁶ lists 26 different factors which can influence drug response in humans. These include well known variables such as age, gender, body weight, liver and kidney function and dietary factors, many of which are well known and are adjusted for, during clinical trials, and also factored into calculations concerning drug dosing.

These variables are the reasons that are used to explain why different patients may respond differently to the same drug. They are the reasons why, similar to several other biological processes, therapeutic outcome data are better described by statistical distributions, rather than discrete values.

Genetic factors offer a significant contribution to inter-patient drug response variability. Estimates at quantifying this genetic contribution have ranged between 20% and 95% for different drugs.^{7,8} Pharmacogenetics is the study of this genetic variability. Its aim is to establish algorithms and models which could be used to associate DNA variations with specific therapeutic outcomes, and therefore use the former to predict the latter. Pharmacogenomics offers

a more global approach, and encompasses the study of variations of DNA and RNA characteristics as related to drug response. Such work is carried out using an “-omics” approach, i.e. using technologies that study the genome (DNA) or transcriptome (RNA) as a global entity rather than focus on localised small candidate regions of interest. The European Medicines Agency, in 2007⁹, offered the definitions shown in Table 2, in order to better clarify the meaning of both terms. Table 3 lists common terminology used in the fields of genetics.

What do pharmacogenetics and pharmacogenomics have to offer?

Throughout the years, the application of therapeutics has gradually shifted focus from the drug to the patient. The “one drug fits all” maxim is no longer valid, and each patient is now the fulcrum around which therapeutic options are specifically selected. Personalized medicine, has thus taken centre stage, and together with evidence-based prescribing, has contributed to significant ameliorations in patient management outcomes.

Table 2: Definitions of the terms “Pharmacogenomics” and “Pharmacogenetics” as approved by the European Medicines Agency.⁹

Pharmacogenomics (PGx)	The study of variations of DNA and RNA characteristics as related to drug response.
Pharmacogenetics (PGt)	The study of variations in DNA sequence as related to drug response.

The application of pharmacogenomic knowledge, aims to expand personalized medicine, by providing a means by which a patient's most individualized variable, his DNA genome, can be used to predict therapeutic outcomes to specific drugs. Adverse effect profiles may also be similarly predicted. Such information has critical value for the selection of the best drug, as well as the best dose, for a particular patient. This can especially afford improved therapy outcomes in patients who are on narrow therapeutic window medications (e.g. anti-epileptic drugs, immunosuppressant agents, theophylline), patients who are being treated with medicines that take a long time to start demonstrating clinical efficacy (e.g. SSRIs) and patients who are on drugs that may exhibit serious adverse reactions (e.g. anti-cancer drugs, anti-retroviral therapy).

The occurrence of serious adverse drug reactions (ADRs), is of major concern in therapeutics, and the major reason for drug withdrawals from the market. A recent Liverpool-based study, reported that 14.7% of hospital admission patients experienced ADRs that were due to drugs that were initiated or continued during the hospital stay¹⁰, while a Swedish-based study reported that 3.1% of deaths in the general population, are the cause of fatal adverse drug reactions.¹¹ ADRs which are due to genetic variation, and which were previously considered to be unpredictable, may now be preventable through pharmacogenetics. Recommendations for applying pharmacogenetic knowledge for ADR prevention include (a) consideration of alternative drugs, whose action is known not to be subject to the genetic variation in question, (b) dose reduction if the prescribed drug is mandatory, (c) advice to the patient to be extra careful to monitor for adverse effects early in therapy, and (d) particular avoidance of administering multiple drugs whose actions are influenced by the same genetic variations (e.g. avoid administering multiple drugs which are metabolised by the same CYP450 enzyme, in patients who carry a low-activity variant for that enzyme).¹² Table 4 lists a few examples of drugs whose adverse effects are well known to be pharmacogenetically dependent. A list of all drugs for which the FDA has requested labelling modifications in order to include pharmacogenetic information may be found on the FDA website.¹³

Ethnic genetic variability

Since pharmacogenetic prediction is based on the association of specific genetic profiles with specific drug responses, the differences in the types and frequencies of DNA variants found in different ethnic groups, often confounds the applicability of testing. For example, a pharmacogenetic test which has been developed from genetic polymorphism data in a Caucasian population, may have been optimized to genotype the 10 most common DNA variants which influence the rate of metabolism of Drug X. However, the Asian population, may only have a few of these variants, and indeed may have others which are not found in Caucasians. This often puts severe constraints on the extent to which pharmacogenetic tests may be put to use, and from a commercial aspect, limits the potential for worldwide distribution of the same testing kit or protocol. The implications of this also have to be seen in a society which is always becoming more and more multinational and multicultural.

How does pharmacogenomic knowledge arise?

Interindividual variations in the human genome are well known. For example, the SNP consortium, a group of ten large pharmaceutical companies and the U.K. Wellcome Trust, has identified about 1.8 million single nucleotide polymorphisms in the human genome.¹⁴ The question which arises is, which of these have any importance to health? Which SNPs are relevant to disease, which are relevant to drug response, and which are completely harmless? And what about other types of genetic variation, such as DNA insertions, deletions and variable repeat sequences?

Initial pharmacogenetic studies have largely applied what is termed the "candidate gene approach." In order to identify how genetics could contribute to the observed interpatient variability to the response of a drug, scientists would need to have detailed knowledge of the mechanism of action of the drug, and then intelligently

Table 3: Common terminology used in genetics

Allele	One of two or more gene variants
Candidate gene	A gene, selected on the basis of being considered important in a particular biological process, and therefore a potentially useful target to study with respect to that process.
DNA microarray	A technique to simultaneously measure several thousand potential alterations within a DNA sample.
Genetic marker	A known location on DNA that can assayed and used, together with several other genetic markers, to characterise an individual. A panel of genetic markers may be used as a "fingerprint" for a particular DNA sample or individual.
Genotype	The genetic makeup of an organism, usually referring to the presence or absence of one or more polymorphisms or mutations.
GWAS	Genome wide association study. A technique to identify which regions in a genome might be responsible for specifically observed features (such as a particular disease or drug response) within a population.
Mutation	A DNA variant sequence that occurs at a frequency of less than 1% in the general population
Polymorphism	A DNA variant sequence that occurs at a frequency of 1% or more in the general population
Phenotype	Features of an organism, which can be measured or observed, such as disease, body weight, response to a drug, eye colour etc.
SNP	Single nucleotide polymorphism. A DNA variation in which one DNA base is substituted by another.

Table 4: Examples of drugs for which pharmacogenetic variability is known to influence the risk of adverse effects^{13,39}

Drug	Gene/s involved	Potential adverse effect
Abacavir	HLA-B*1502	Increased risk of general hypersensitivity
Azathioprine	TMPT	Slower metabolism and greater risk of myelotoxicity
Carbamazepine	HLA-B*1502, CYP1A2	Increased risk of severe dermatological hypersensitivity reaction
Carvedilol	CYP2D6	Increased risk of adverse effects in slow metabolizers
Clopidogrel	CYP2C19	Reduced metabolism of the pro-drug clopidogrel, lower exposure to the active metabolite and lower therapeutic effect
Fluoxetine	CYP2D6	Increased risk of toxicity in slow metabolizers, especially if prescribed with other CYP2D6-metabolized drugs
Irinotecan	UGT1A1	Slower metabolism and increased risk of neutropenia
Isoniazid	NAT2	Increased risk of agranulocytosis, hepatotoxicity and seizures
Nilotinib	UGT1A1	Exacerbation of drug-induced jaundice
Rifampicin	NAT	Slower metabolism and greater risk of general adverse reactions
Warfarin	CYP2C9, VKORC1	Reduced metabolism and higher bleeding risk

select critical steps in the pathway to study genetically, based on the presumption that such steps are where it is most likely that genetic variability might have a phenotypic response. Any identified polymorphisms have then to be studied from a functional aspect, in order to prove that this variability is indeed responsible for the observed drug response variation. This has generated considerable valid data and indeed up to about 10 years ago, published studies in the pharmacogenetic scientific literature are largely based on such approaches. However the failure to identify pharmacogenetic

variability cannot be underestimated in such studies. The fact is that we do not know all the mechanisms of action of every drug, and a cursory look through any scientific literature database will show that even today, scientists are still identifying novel pathways for therapeutic or adverse effects of established drugs which have now been marketed for several years.

With the advent of new research technologies, the candidate gene approach has now been making way for a newer *pharmacogenomic* approach, which does not rely on prior knowledge of mechanism

of drug action. This approach is based on what are termed genetic *association* studies, and from a pharmacological knowledge aspect, only require the clinical ability to be able to stratify patients into separate categories, based on how they respond to a particular drug. A group of patients, may for example, be prescribed a drug, and based on the therapeutic outcome, be grouped into poor responders, normal responders and high responders. A DNA sample from each patient is then screened for thousands of *genetic markers* spread throughout the whole genome, using a technological approach called a *DNA microarray* system. These markers are actually regions of DNA that have been well localized and studied, are known to be polymorphic (ie are likely to be different in different individuals), and are distributed throughout the whole genome. The most common type of markers used, are indeed SNPs. For the purposes of association studies, such markers may be compared to thousands of signposts, spread throughout the whole genome, with the technological ability for the message on every individual signpost to be accurately assayed and read using microarrays. The marker data from each patient is then analysed statistically, with the aim of identifying a small set of DNA markers that are statistically *associated* with a particular patient response group for the drug under study. Since these DNA markers can be easily genotyped, this approach generates a shortlist of DNA markers

Table 5: Drugs for which dose adjustment could be considered based on Amplichip® CYP450 assay results

Drugs which are substrates for CYP2D6	
β-blockers	Carvedilol, metoprolol, propafenone, timolol
Anti-depressants	Amitriptyline, clomipramine, desipramine, imipramine, paroxetine, venlafaxine
Antipsychotics	Haloperidol, risperidone, thioridazine
Opioids	Codeine, dextromethorphan, tramadol
Others	Atomoxetine, flecainide, mexiletine, ondansetron, tamoxifen
Drugs which are substrates for CYP2C19	
Proton pump inhibitors	Omeprazole, lansoprazole, pantoprazole
Anti-epileptics	Diazepam, phenytoin, phenobarbitone
Others	Amitriptyline, clomipramine, cyclophosphamide, progesterone

(essentially DNA polymorphisms) which can be assayed for any new patient, and which are statistically robust to be able to be used to predict into which therapeutic category (poor, normal or high responders, in this example) the patient will fall. This approach forms the basis of what are known as pharmacogenomic genome wide association studies (GWAS). Although more expensive than candidate gene approaches, GWAS have the advantage of not relying on the extent of available pharmacological knowledge of drug action, and have a higher success rate in establishing genetic profiles which are predictive of therapeutic or adverse reaction outcomes.

Pharmacogenetics, pharmacogenomics and pharmacy

Perhaps one of the greatest challenges of science is to bridge the gap between theory and practice. Rather than simply a matter of education, this is often more a question of implementation. Professionals within a health care system need to be informed about new therapeutic potentials, they need to be given access to information they can assimilate and they also need to be part of the implementation process of any novel tool. Both pharmacists and medical doctors need to understand, appreciate, and advise; and be knowledgeable enough to apply emerging pharmacogenetic principles, and interpret their outcomes.

“The main role of pharmacists within both primary and secondary care, is to supply medicines and to ensure this medication is appropriate for the individual and taken safely.”¹⁵ Within this context, pharmacists will need to take on new roles in the realm of pharmacogenetics, and should be in a position to pioneer the introduction of new tools as they are made available. This may not only require occasional participation at appropriate structured educational programmes, but also personal initiative to keep up to date with this rapidly developing field. As early as 2003, it was already recognised in the UK, that the level of genetics in most pharmacy undergraduate curricula was insufficient to empower newly emerging pharmacists with the skills required for the future.¹⁶ Similar observations were also made on pharmacy curricula in the US, at around the same time.^{17,18} Pharmacogenetics is unfortunately still often viewed by academic curriculum planners, to be an intellectual area of study, with few current practical implications, and is

therefore relegated to a lower priority level than, for example, pharmacodynamics and pharmacokinetics, both of which are widely recognised to merit a serious understanding, if one is to appreciate therapeutic and toxicological drug actions. However, as early as 2002, a US questionnaire-based study carried out amongst various health care professionals, had already identified a high level of awareness that Pharmacogenetics will be useful to “identify patients who will respond to a medication”, it will “identify patients who are at high risk for adverse drug events and it will help to “determine a medication’s place in therapy.”¹⁹

Perhaps one reason for the relative low direct health care professional involvement at the current time, is the specialization of therapeutic areas in which clinical applications of pharmacogenetic testing are currently available. The translational period from bench to bedside is naturally long, and as expected, priority has been afforded to therapeutic areas for which it is more critical for outcomes to be optimized, such as oncology. This effectively places the focus of pharmacogenetics on hospital and specialized clinics, and less on the community. Such focus is however expected to change, as more evidence for the benefits of genotype-guided prescribing emerges, and more pharmacogenetic tests become available.

Indeed, the 2006 report entitled ‘Realising the Potential of Genomic Medicine’, published by the Royal Pharmaceutical Society of Great Britain²⁰, already highlighted the importance of augmenting the pharmacists’ professional knowledge of pharmacogenetics and molecular medicine, in order to be prepared for new pharmacogenetic roles. Such roles may vary according to the pharmaceutical setting. Pharmacists working in drug development may be involved in the design and execution of pharmacogenetic arms of pre-marketing clinical trials, hospital clinical pharmacists may be involved in the prescription of pharmacogenetic tests, while community pharmacists might be more involved in providing information and advice on drug use, in connection with already available patient pharmacogenetic test results. In all cases, a sound knowledge of pharmacogenetic approaches, together with training in the correct interpretation of a pharmacogenetic test result, and its significance in pharmaceutical practice, is mandatory.²¹

Pharmacogenetics and pharmacogenomics in practice

Translational pharmacogenetics / pharmacogenomics is evolving. As selected pharmacogenomic biomarkers are promoted from “exploratory” to “qualified” status²², more approved tests will become available. The following are some robust examples of cases where pharmacogenetic testing has already been integrated into therapeutic drug use.

Isoniazid

Perhaps the earliest and most widely reported pharmacogenetic data, was that concerning the anti-tuberculous agent isoniazid (INAH). Isoniazid is a substrate for metabolism by acetylation through the actions of N-acetyltransferase type 2 (NAT2). The existence of fast and slow acetylating individuals has been known for decades, and interindividual variations in the INAH elimination half life of over 100% have been reported. INAH dose adjustment based on NAT2 phenotype status, has been well studied in the literature, and this was initially based on phenotypic differentiation identified by biochemical tests. Slow acetylators require dose reduction, in order to avoid development of potentially serious adverse drug reactions such as agranulocytosis, hepatotoxicity and seizures, while fast acetylators require increased doses to attain therapeutic efficacy.²³ Extensive NAT2 pharmacogenetic studies have now identified specific gene variants that are responsible for fast acetylators and slow acetylators, thus replacing phenotype testing with genotype testing as a basis for determination of INAH acetylator status.

Trastuzumab

Trastuzumab (Herceptin®) is a humanized monoclonal antibody against the HER2 tyrosine kinase receptor, which is overexpressed in 25-30% of breast cancers. HER2 overexpression (HER2+) is associated with enhanced tumour aggression. Clinical studies have shown Trastuzumab to be effective in HER2+ patients, but only exert insignificant effects in HER2- individuals. Thus the establishment of HER2 status has become an important determinant to the use of Trastuzumab. Modern approaches to determine HER2 status, today include immunohistochemistry to semi-quantitatively estimate the amount of HER2 proteins expressed on the surface of tumour cells, FISH (Fluorescence In-Situ Hybridization)



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Table 6: Useful pharmacogenetics and pharmacogenomics websites.
All listed websites are live as on 30 May 2011

European Medicines Agency Pharmacogenomics Working Party http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000018.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028d91&jseabled=true
Food and Drug Administration Interdisciplinary Pharmacogenomics Review Group http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083889.htm
PharmGKB Pharmacogenomics knowledge base http://www.pharmgkb.org/
National Center for Biotechnology Information: One size does not fit all: the promise of pharmacogenomics http://www.ncbi.nlm.nih.gov/About/primer/pharm.html
The International Union of Basic and Clinical Pharmacology. Pharmacogenomics and Pharmacogenetics: Introduction http://www.iuphar.org/sections/PGx/sec_PGx.html
Nuffield Council on Bioethics. Pharmacogenetics: ethical issues. http://www.nuffieldbioethics.org/pharmacogenetics
National Institute of Health. National Institute of General Medical Sciences. NIH Pharmacogenomics Research Network. http://www.nigms.nih.gov/Research/FeaturedPrograms/PGRN/
NHS, UK. National Genetics Education and Development Centre. Teaching pharmacogenetics. http://www.geneticseducation.nhs.uk/teaching-genetics/pharmacogenetics.aspx
PHG Foundation interactive tutorials. Pharmacogenomics. http://www.phgfoundation.org/tutorials/pharmacogenomics/index.html

to determine the number of copies of HER2 genes in tumour cells, and the SPoT-Light HER2 CISH (Subtraction Probe Technology Chromogenic In Situ Hybridization) test, which also detects the number of HER2 gene copies in cancer cells, but is simpler to perform than FISH, and was approved by the FDA as a HER2 screening test in 2008.²⁴

Substrates of CYP2D6 and CYP2C19

The two major cytochrome P450 enzymes, 2D6 and 2C19 are estimated to contribute to the metabolism of approximately 25% of currently used prescription medicines in Europe. These enzymes are highly polymorphic, and several variants of their genes exist. Some gene variants result in enzyme proteins with similar activity to wild type, but most are responsible for enzymes with higher or lower activity than normal. Indeed, some variants produce an enzyme with no activity at all. Specific technical details may be found through the Human Cytochrome P450 Allele Nomenclature

Committee.²⁵ Therefore the rates of metabolism of drug substrates for CYP2D6 and CYP2C19 are greatly dependent on the particular gene variants which an individual is carrying.

Excessive or prolonged therapeutic effect or even drug-related toxicity may follow administration of a *typical* dose to a patient who carries a low-activity variant, by failing to metabolize the drug at the expected rate. Conversely, a patient with a high activity variant, may metabolize the drug at a faster rate than normally expected, and may be therefore potentially unable to maintain therapeutic window concentrations of the drug, at conventional dosing regimens. Adjustment of drug dosage could therefore be required, based upon knowledge of CYP2D6 and CYP2C19 genotypes.

In view of this, Roche® developed a DNA microarray assay (using Affymetrix® technology) that genotypes for 27 selected CYP2D6 and 3 selected CYP2C19 gene variants, and based on this data, predicts

the metabolizer status of the individual. The test generates a predicted phenotype of ultrarapid, extensive, intermediate or poor metabolizer status, for CYP2D6 and extensive or poor metabolizer status for CYP2C19. Table 5 lists a selection of CYP2D6 and CYP2C19 substrates, which Roche® recommends be suitable predictive targets for the application of this test. The Amplichip test was approved by the FDA in 2004.²⁶

Irinotecan

Irinotecan is a topoisomerase I inhibitor anti-cancer drug, normally used in combination with other chemotherapy agents. Its main indication is colon cancer, and patients may experience severe diarrhoea, neutropenia and immunosuppression as relatively common serious adverse effects. Following administration, the drug is initially hydrolysed to its active metabolite SN-38, and subsequently inactivated in the liver by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). This latter inactivation step, is under the influence of a much studied promoter DNA variant which involves the insertion of an additional TA dinucleotide in a tandem repeat sequence. Patients carrying this variant, known as UGT1A1 allele 28 (UGT1A1*28, (TA)₆>(TA)₇), produce less UGT1A1 than normal, and therefore take longer to metabolize irinotecan than expected. Such patients are at a higher risk of potentially fatal irinotecan toxicity.²⁷ This has led to the commercialization of an FDA-approved UGT1A1 genotyping assay²⁸, and an FDA approved amendment to the official prescribing information which states that "Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia" and that "when administered in combination with other agents, or as a single-agent, a reduction in the starting dose should be considered for patients known to be homozygous for the UGT1A1*28 allele."²⁹

Warfarin

Warfarin is a prime example of a commonly used drug, possessing significant inter-patient response variability, a narrow therapeutic window, and the potential to adversely interact with a wide range of concomitantly administered medicines. Patients on warfarin need to be regularly and individually monitored using the international normalized ratio (INR) as

an index of warfarin efficacy, and doses need to be regularly optimized in order to maintain effectiveness and minimize adverse reactions.

Published studies have suggested that over 40% of interindividual warfarin dose variability can be predicted by SNPs in the VKORC1 (1639G>A and 1173 C>T alleles) and CYP2C9 (CYP2C9*2 and CYP2C9*3 alleles) genes. VKORC1 codes for subunit 1 of the warfarin target, Vitamin K epoxide reductase complex, while CYP2C9 partakes in the metabolism of both R- and S-warfarin enantiomers. Carriers of variant alleles are at higher risk for bleeding complications,³⁰ particularly at induction of warfarin therapy, and genotype-guided dosing algorithms have been shown to be safer and more effective at estimating the maintenance warfarin dose rather than INR monitoring alone.³¹

Regulatory issues

The year 2005 saw the establishment of the European Medicines Agency Pharmacogenetics Working Party (PgWP; this later changed its name to the Pharmacogenomics Working Party)³² and the Food and Drug Administration Interdisciplinary Pharmacogenomics Review Group (IPRG).³³ Both groups work jointly, to prepare guidelines and provide advice; and extensive information about their activities can be found on their respective websites.³⁴ One of the major actions of these groups has been the establishment of "Voluntary Exploratory Data Submission" (VXDS) procedures (previously called "Voluntary Genomic Data Submission" or VGDS). VXDSes constitute pharmacogenomic submissions that are not required as part of a regulatory submission, and therefore are not part of the regulatory decision making processes. They provide a platform through which industry is encouraged to voluntarily submit pharmacogenomic data to the EMA / FDA, with the aim of benefitting from an enhanced mutual understanding of relevant scientific issues. Such understanding "may prevent delays in reviews of future submissions where genomics are an integral part of specific studies in a drug development program."³³ VXDS submissions address areas such as the genetic loci or gene expression profiles being explored, the

Pharmacogenetics practice points for pharmacists

- DNA variations may be responsible for inter-patient differences in drug efficacy and toxicity.
- One specific DNA variant may influence the response of several drugs.
- Variations in genes which code for drug receptors, drug transporters, metabolising enzymes, and proteins involved in signalling pathways may be especially relevant.
- Pharmacogenetics aims to predict drug response from patient genotypes, and therefore provide a tool for personalized optimization of drug and dose selection.
- A specific pharmacogenetic test is usually only applicable to the population for which it was developed, and not to other ethnically diverse groups.
- The correct interpretation of some pharmacogenetic tests may require prior genetics-based knowledge and training.
- The EMA and the FDA are both actively involved in ongoing developments, through the establishment of the PgWP and IPRG groups.

test systems and techniques employed, the application of pharmacogenomic testing during drug development, procedures for transmitting, storing, and processing large complex data sets, and bioinformatics software development.²² The first joint FDA / EMEA document, detailing the general principles to be applied in processing joint FDA / EMEA VGDSes was issued as early as 2006³⁵, just one year after the establishment of the PgWP and IPRG working groups.

Clinical implementation of pharmacogenetics

The Pharmacogenomics Research Network of the National Institutes of Health, USA, set up a Clinical Pharmacogenetics Implementation Consortium (CPIC) in 2009, with the aim of addressing the "need for very specific guidance to clinicians and laboratories so that pharmacogenetic tests can be used wisely in the clinic." In its two years of existence, the CPIC has set up frameworks aimed at "understanding the types and levels of evidence needed to justify incorporation of pharmacogenetics into clinical practice." In particular, CPIC assign importance to the following considerations (a) a sound scientific rationale linking genomic variability with drug effects, (b) the therapeutic index of the involved medications, (c) the severity of the underlying disease, (d) the availability of alternative dosages or drugs for patients with high-risk genotypes, (e) the availability of approved laboratory tests, and (f) the availability of peer-reviewed

clinical practice guidelines that incorporate pharmacogenetics in their recommendations. Electronic databases are set to be critically instrumental for such implementation, together with decision-support tools which will aim to integrate database information with laboratory pharmacogenetic test results. This can provide a platform through which genetic data can be translated to clinical practice.³⁶

Future developments could see actual genetic testing moving out of the laboratory and into the clinic. The Imperial College, London, and its spinout company DNA Electronics, are currently developing a novel handheld device that provides on-the-spot pharmacogenetic testing. This device, called the "SNP Dr" uses DNA from saliva or cheek swab samples as a template for analysis, and performs rapid SNP assays based on a novel silicon chip technology, to provide "while you wait" pharmacogenetic predictions.³⁷ Such technology, will undoubtedly accelerate the integration of pharmacogenetic principles within rational prescribing practices.

Conclusion

Pharmacogenetics is an evolving discipline. The ongoing co-operation of basic and clinical research with evidence-based science and regulatory frameworks will help to achieve controlled implementation of a system which is working to provide new tools for improved therapeutic outcomes, and safer prescribing patterns. Table 6 lists some relevant websites, for further reading.

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The role of prostanoids in the modern management of glaucoma

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Educational Aims

- To identify the role of prostanoids in glaucoma
- To highlight the mode of action and advantages of the latest drug therapy
- To better appreciate clinical applications and awareness of side effects
- To better understand combination therapy and its advantages

Keywords

Intraocular pressure (IOP), glaucoma, prostanoids, prostaglandin analogues, prostamide

The history of glaucoma pharmacology begins in 1862 with the isolation of physostigmine from the calabar bean.¹ The discovery of epinephrine's intraocular pressure lowering capacity came just after WWI. During the 20th century, drug discovery and development accelerated, with the introduction of carbonic anhydrase inhibitors, beta-blockers (1970s), alpha-agonists and lately prostanoids(1990s).² Prostanoids have been divided into PG analogues and prostamides because of differences in molecular structures. The drugs share a novel mechanism of action that produces a potent ocular hypotensive effect and a novel local adverse effect of increased iridial pigmentation. Anti-glaucoma medication targets different key pathophysiological aspects of the disease and overlap in the mechanisms of action of these drugs proved to be important. The development of a completely new class of drugs added to the suppressive armamentarium against this blinding condition. More drug variety skewed glaucoma care away from the theatre, effectively changing the timing of glaucoma surgery.

Pharmacology of prostaglandin analogues

These drugs are lipid structural derivatives and are synthetic prostaglandin F2a analogues.³ They are actually prodrugs and these arachidonic acid derivatives are hydrolyzed by corneal esterases to a biologically active free acid. Bimatoprost is a subclass and is actually a prostamide rather than a prostaglandin analogue. Prostamides do not appear to bind to prostaglandin FP receptor as PG analogues.

Mechanism of Action

Prostaglandin analogues increase uveoscleral outflow rather than altering conventional trabeculo-canalicular aqueous outflow.⁴ The IOP-lowering effect of latanoprost lasts for 20 to 24 hours after a single dose, which allows a single daily dosage regimen. Data from four randomized double-masked multicentre studies indicate that a once daily dose of topical latanoprost 0.005% is as effective as timolol 0.5% twice daily in the treatment of patients with primary open-angle glaucoma or ocular hypertension.⁵

Uveoscleral outflow is enhanced because of:

- Ciliary body muscle relaxation
- Dilation of spaces between ciliary muscle bundles
- Altered metabolism of the extracellular matrix surrounding the ciliary muscle cells (modulation of tissue matrix metalloproteinases)
- Altered cellular morphology.⁶

Uveoscleral outflow does not end in the episcleral venous circulation so it is possible to get an intraocular pressure around episcleral venous pressure (~10mmHg).⁷ This is very important especially in normal tension glaucoma where optic nerve damage occurs in the presence of lower intraocular pressures.

Bimatoprost is an active drug in contrast to latanoprost and travoprost which, as described above, require activation by corneal enzymes. Bimatoprost increase aqueous outflow by increasing both trabecular outflow facility and uveoscleral outflow.

Latanoprost 0.005% once daily was compared to timolol 0.5% twice daily in three large studies. The former reduced the IOP by around 30% and was found to be predominantly more effective than the beta-blocker. Peak effect of PG analogues occurs 12 hours post-instillation. There was no loss of effect after a year. Travoprost is very similar to latanoprost, though the

Table 1. Commercially available prostanoids in drop form

<i>commonly used</i>	<i>concentration of drug per drop</i>
Latanoprost	0.005%
Travoprost	0.004%
Bimatoprost	0.03%
<i>Less commonly used</i>	
Unoprostone	0.15%
Tafluprost	0.0015%

former binds to the FP receptor with a higher affinity. They have the same mechanism of action and are prescribed once daily, preferably in the evening.⁸

Bimatoprost was also compared to timolol and was found to be much more superior in efficacy. An interesting trial comparing the three drugs for 12 weeks found no statistical significance in the difference of IOP lowering, however in the long term (6months), bimatoprost was found to be more effective. Some glaucoma specialists postulate a switch from one prostanoid to another. This was hinted at in a study that showed that patients who were not responsive to latanoprost have a likelihood of 13/15 of obtaining at least 20% reduction in IOP if switched to bimatoprost.⁹ In certain situations one might also combine a prostaglandin analogue with the prostamide bimatoprost, especially in the presence of multiple intolerance to other anti-glaucoma medications.

There is evidence that latanoprost lowers IOP in angle-closure glaucoma and its efficacy is not related to angle width.¹⁰

Role of Combination therapy

Combining an aqueous suppressant with a prostaglandin analogue enhances IOP-lowering effect as both aqueous inflow and outflow are targeted. For example, combining latanoprost 0.005% once daily with timolol 0.5% twice daily achieves 13-30% increase in IOP-lowering effect.¹¹

Prostaglandin analogues side effects

Table 2 shows an exhaustive list of known side-effects of prostaglandin analogues.

More specific side-effects

Iris pigmentation¹² - Eyes with a concentric heterochromia (more pigment around the pupil than in the periphery) before treatment are more at risk of iris pigmentation. Eyes that already have more iris melanocytes are more prone to pigmentation. Hence green-brown eyes are more at risk than blue or blue-grey irises. PG analogues do not cause iris melanocyte proliferation but merely stimulate these cells to produce more melanin hence making this iris look darker.¹³ Iris pigmentation is irreversible and seems

to be least associated with bimatoprost. Iris naevi are not affected by PG analogues.

Hyperaemia¹⁴ This is conjunctival injection which is not related to an allergic follicular conjunctival response or actual tissue inflammation. The bimatoprost-related hyperaemia was mild to moderate and only 4% of patients using this drug stopped treatment because of this. This hyperaemia is sometimes compounded with a burning sensation and occurs primarily at the initial stages of treatment and eventually improves. Clinical examination did not show an increased anterior chamber flare.

Meibomian gland disease is slightly more prevalent with prostaglandin analogues because they may stimulate meibomian gland secretion which may predispose to the formation of chalazia and seborrhoeic blepharitis.¹⁵

Eyelash growth - Some consider this as a beneficial side-effect. Some recent topical preparations exist which contain a prostaglandin analogue to minimize radiation-induced eyelash loss in an oncological setup.¹⁶

Prostaglandin analogues increase the risk of macular oedema because there is evidence that they alter blood-ocular barrier especially in pseudophakic and aphakic patients.¹⁷

Periorbital fat atrophy.¹⁸ This visually noticeable side effect has features demonstrable on MRI scanning. The periorbital fat atrophy is most apparent with unocular use and both doctors and patients need to be aware of this side effect before commencing treatment. The effects, however, appear to be reversible with treatment cessation.

Systemic safety of prostaglandin analogues

Latanoprost has a plasma half-life of 17 minutes and is administered in very low doses so only minimal side effects are anticipated. No effect was found on cardiovascular integrity, metabolic function and the haematologic profile of the human body.

Tafluprost

Tafluprost is a recent addition to the prostaglandin analogue spectrum of drugs and is already commercially available. Early studies comparing tafluprost with the earlier travoprost 0.004% found that travoprost 0.004% monotherapy produced lower diurnal IOP than tafluprost 0.0015% in patients with primary open-angle glaucoma or ocular hypertension, but exhibited a similar safety profile.¹⁹

Table 2. Prostaglandin analogues side effects

Side Effect	Incidence/comment
<i>Non-specific</i>	
Conjunctival hyperaemia	36%, more prominent with bimatoprost
Burning and stinging	25%
Blurred vision	17%
Pruritus	15%
Foreign body sensation	33%
Tearing	6%
Ocular pain	13%

When to use what type of Prostanoid

It is important to be aware that not all these types of prostanoids were available to prescribe all at once and historically molecular modifications were implied so as to make the newer drug more efficient with less potential side-effects. As pointed above, all the prostanoids have similar therapeutic effects but overall they changed the approach of treating glaucoma, as it was found out that they are very effective as first-line drugs.²⁰

Conclusion

The introduction of a new class of IOP-lowering drug with a completely different mode of action to the already existing ones slows down the pathophysiological process of this optic neuropathy. High intraocular pressure is one of the most prominent risk factors for the development of glaucoma. Anomalous ocular blood flow orchestrated by endothelin also contributes to this disease progression. Current studies are on the go to identify new molecular structures that have anti-endothelin effects in the context of disease progression in glaucoma in patients with a normal intraocular pressure.

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Key points

- The drugs share a novel mechanism of action that produces a potent ocular hypotensive effect.
- Prostaglandin analogues increase uveoscleral outflow rather than altering conventional trabeculo-canalicular aqueous outflow.

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NAME OF THE MEDICINAL PRODUCT VIAGRA 25 mg, 50 mg, 100 mg film-coated tablets **QUALITATIVE AND QUANTITATIVE COMPOSITION** Tablet 25 mg: Each tablet contains 25 mg of sildenafil (as citrate). Excipient: Lactose. Tablet 50 mg: Each tablet contains 50 mg of sildenafil (as citrate). Excipient: Lactose. Tablet 100 mg: Each tablet contains 100 mg of sildenafil (as citrate). Excipient: Lactose. **PHARMACEUTICAL FORM** Tablet 25 mg: Film-coated tablet. Blue rounded diamond-shaped tablets, marked "PFIZER" on one side and "VGR 25" on the other. Tablet 50 mg: Film-coated tablet. Blue rounded diamond-shaped tablets, marked "PFIZER" on one side and "VGR 50" on the other. Tablet 100 mg: Film-coated tablet. Blue rounded diamond-shaped tablets, marked "PFIZER" on one side and "VGR 100" on the other. **THERAPEUTIC INDICATIONS** Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for VIAGRA to be effective, sexual stimulation is required. **POSLOGY AND METHOD OF ADMINISTRATION** For oral use. Use in adults: The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If VIAGRA is taken with food, the onset of activity may be delayed compared to the fasted state. Use in the elderly: Dosage adjustments are not required in elderly patients. Use in patients with impaired renal function: The dosing recommendations described in 'Use in adults' apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 ml/min). Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg. Use in patients with impaired hepatic function: Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg. Use in children and adolescents: VIAGRA is not indicated for individuals below 18 years of age. Use in patients using other: With the exception of ritonavir for which co-administration with sildenafil is not advised a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors. In order to minimise the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated. Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure). VIAGRA is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section Special Warnings and Precautions for Use). The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases). **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered. Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g. aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure. VIAGRA potentiates the hypotensive effect of nitrates (see section Contraindications). Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of VIAGRA without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors. Agents for the treatment of erectile dysfunction, including sildenafil, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia). The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended. Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking VIAGRA and consult a physician immediately (see section Contraindications). Co-administration of sildenafil with ritonavir is not advised. Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section Posology and method of administration). In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms. Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitropruside in vivo. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment. The film coating of the VIAGRA tablet contains lactose. VIAGRA should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. VIAGRA is not indicated for use by women. **UNDESIRABLE EFFECTS** The safety profile of VIAGRA is based on 8691 patients who received the recommended dosing regimen in 67 placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion. Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >9 years. Because not all adverse reactions are reported to the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined. All medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by frequency (very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000). In addition, the frequency of medically important adverse reactions reported from post-marketing experience is included as not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance: Very common (>1/10): Headache. Common (>1/100 and <1/10): Dizziness, visual disorders, visual colour distortion, flushing, nasal congestion, dyspepsia. Uncommon (>1/1,000 to <1/100): Somnolence, hypoaesthesia, conjunctival disorders, eye disorders, lacrimation disorders, other eye disorders, vertigo, tinnitus, palpitations, tachycardia, vomiting, nausea, dry mouth, skin rash, myalgia, chest pain, fatigue, heart rate increased. Rare (>1/10,000 to <1/1,000): Hypersensitivity reactions, cerebrovascular accident, syncope, deafness*, hypertension, myocardial infarction, atrial fibrillation, epistaxis. Not known: Transient ischaemic attack, seizure, seizure recurrence, non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion, visual field defect, ventricular arrhythmia, unstable angina, sudden cardiac death, Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), priapism, prolonged erection*, Ear disorders: Sudden deafness. Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. **SUPPLY CLASSIFICATION** POM **MARKETING AUTHORISATION HOLDER** Pfizer Limited, Sandwich, Kent CT13 9NJ, United Kingdom **LOCAL REPRESENTATIVE OF THE MARKETING AUTHORISATION HOLDER**: V.J. Salomone Pharma Ltd., Upper Cross Road, Mansa MRS 1542, Tel : +356 21220174 **MARKETING AUTHORISATION NUMBER(S)**: EU168077702-019 **DATE OF REVISION OF THE TEXT** 01 July 2010. For additional information please refer to the full Summary of Product Characteristics



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Herbal medicines: adverse effects and drug-herb interactions

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Educational Aims

- To help clear the 'myth' that herbal medicines are entirely safe as they are derived from natural sources.
- To provide an overview of the different, potential types of drug-herb interactions.
- To highlight the importance of asking patients about herbal medicine use and to check for any possible interactions with their medications.

Key words

Herbal medicines, adverse effects, interactions, drug-herb interactions

With the aim of moving away from the 'synthetic' world towards a more 'organic' world, patients are increasingly seeking herbal remedies to self-treat medical conditions. Most clinicians are oblivious to their patients' use of herbal medicine. All medicinal agents have potentially unexpected effects including toxicity and interactions, and herbs are no different. Drug-herb interactions are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. Herbal medicines do not need to be avoided, the only fundamental issue is that they should be considered as medicine and the adverse effects and potential interactions considered. Thus pharmacists and doctors should be better informed to minimise patient harm.

Definition and Description

For centuries before the beginning of scientific medicine, traditional medicine of various cultures around the world employed the use of medicinal plants as disease remedies. Products made from plants that are used to maintain or improve health have been called herbal medicines, remedies, supplements, botanicals or phytomedicines.^{1,2}

Herbal Medicine may therefore be defined as:

*Plant derived material or preparations with therapeutic health benefits, which contain either raw or processed ingredients from one or more plants(WHO 2005).*³

Introduction

With limited regulatory oversight and strong advertising, many herbal products have made their way into pharmacies and health shops and into patients' self-prescribed therapy. The internet has also become part of the marketplace. With the aim of moving away from the 'synthetic' world towards a more 'organic' world, patients are increasingly seeking herbal remedies to self-treat medical conditions, complement conventional therapies, and maintain their overall health and well-being.^{2,4}

Most patients receive their information about herbs and supplements from sources other than their healthcare provider.^{2,4} Clinicians are often oblivious to their patients' use of herbal medicines for a variety of reasons. Being natural products, patients wrongly believe they are always safe, others fear that healthcare professionals may have negative attitudes towards their use and do not report using such remedies to avoid confrontations. In addition, healthcare professionals are often not likely to ask patients about their self-medication.^{2,4}

Negative effects can result from this lack of communication, which could include adverse effects or drug-herb interactions.^{1,4} Patients may also substitute herbal remedies for more conventional therapies without informing their doctor.²

Recently, most often unaware to both the healthcare professional and the patient, several dietary and multi-vitamin supplements began to introduce herbs into their preparations. Preparations for improved joint function, improved performance, hair and eye supplements, sleep aids, weight loss and advancing age are among the preparations which are including herbs. Hence, herbal medicines may also be

consumed by those patients who did not specifically request their use.

Adverse effects and Interactions

All medicinal agents have potentially unexpected effects including toxicity, and herbs are no different.^{1,2,4-11} As with other drugs, the risk of unexpected effects may be influenced by a user's age, gender, genetics, nutrition status, and concurrent disease states and treatments.^{2,4,9} In clinical practice recognizing adverse effects of herbal medicine is not routine and their reporting is even less frequent.^{2,4-9}

It is important to be aware of any substances that have the potential to cause toxicities and to interact with prescribed medications. Most adverse reactions involve the skin, liver, GI tract but can involve the heart (e.g.ephedra). Significant hepatotoxic effects were reported with kava or echinacea when taken concurrently with other hepatotoxic drugs. The use of a drug and a herb that are both associated with potential hepatotoxic effects should be avoided.²

Even less is known about interactions than about adverse effects and much is based on speculation or on theoretical interactions rather than evidence-based and many have only been observed *in vitro* and not *in vivo* (Table 2)⁵⁻⁹ It is important to note that *in vitro* effects are not necessarily replicated *in vivo*. Findings *in vivo* often appear weaker than those *in vitro* which would suggest that a clinical study is warranted.⁹

An interaction may involve having the herb component to cause an increase/decrease in the amount of drug in the blood stream.^{5,6,9} Drug-herb interactions are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions.^{1,5,8,9}

Pharmacokinetic Interactions

Absorption

Interactions affecting absorption result in a reduction/increase of the absorption of the drug.¹⁻⁹ Changes in intestinal pH, complexing mechanisms and drugs affecting intestinal motility will affect absorption.⁵ For example, herbs such as aloe leaf, guar gum and senna, which are common ingredients in herbal weight-loss products, exert a laxative effect that may decrease intestinal transit time and reduce drug absorption. St. John's Wort induces intestinal P-glycoprotein, which may decrease the absorption of

common P-glycoprotein substrates, such as digoxin.^{5,6,8,9} Such effects may be reduced if the drug is consumed 1 hour before or 2 hours after the herb.¹

Distribution

A drug with high plasma protein binding (e.g. warfarin, carbamazepine) that has a small volume of distribution may be displaced by a herb competing for the same binding sites.^{1,5,6,8} Drug displacement from protein-bound forms, by concurrent drug administration, causes an increase in serum drug levels and which may lead to an increase in therapeutic effect.^{2,5,8}

Metabolism

Enzyme Induction

A decrease in the amount of drug could occur

by stimulating the production and activity of enzymes that degrade the drug and prepare it for elimination from the body.^{2,5,8,9} Such is the case with St. John's Wort which induces the cytochrome P450 enzymes which are responsible for the metabolism of several drugs.^{1,2,4-11} This is a common mechanism and applies to the way in which St. John's Wort may reduce the efficacy of the oral contraceptive pill or blood levels of warfarin, digoxin, protease inhibitors, theophylline, carbamazepine.^{4,5-11}

Enzyme Inhibition

The opposite may also occur, in which the herb inhibits the production of the enzyme required to break down the drug, hence increasing the drug levels.^{5,8,9} Unlike enzyme induction, which may take several days or

Table 1: Recommended Herbal Medicine References

National Center for Complementary and Alternative medicine. CAMCitationIndex.

Available at: <http://nccam.nih.gov/health/herbsataglance.htm>

Literature citations (with abstracts) of all aspects of alternative medicine. Free.

NIH Office of Dietary Supplements. IBIS Database. Available at: <http://ods.od.nih.gov/>

Literature citations (with abstracts) of dietary supplements including vitamins, minerals, and botanicals. Free.

Alternative Medicine Foundation, Inc. HerbMed. Available at: <http://www.herbmed.org/index.asp>

Online monographs of 20 popular herbal products. Literature-based reviews with references. Free. Subscription required to view entire database (233 herbs).

Natural Medicines Comprehensive Database. Available on: <http://www.nlm.nih.gov/medlineplus/druginfo/natural/607.html>

Provides online monographs of popular herbs. Free.

World Health Organisation, Geneva. 2011. Available on: <http://apps.who.int/medicinedocs/en/d/Js2200e/>

Provides online monographs of 90 popular herbs. Free.

Baxter K, Driver S, Williamson E. Stockley's herbal medicines interactions. London:Pharmaceutical Press;2009.

Literature-based review of more than 150 herbs with particular reference to their interaction profile. Online version available with subscription on *MedicinesComplete* (<http://www.medicinescomplete.com>)

Barnes J, Anderson LA, Phillipson JD. Herbal medicines: A guide for health care professionals. London: Pharmaceutical Press; 2007.

Herbal monographs. Literature-based reviews with references. Online version available with subscription on *MedicinesComplete* (<http://www.medicinescomplete.com>)

Fetrow CW, Avila JR. Professional's handbook of complementary and alternative medicines. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2004.

Herbal monographs. Literature-based reviews with references.

Table 2: Herb-Drug Interactions of particular concern

(N.B.This is not an exhaustive list. Many reactions are theoretical and have only been observed *in vitro*)^{1,4,5,6,9-15}

Drug or Drug Class	Herb(s)	Effect
Anaesthetics	Kava, Hawthorn, St John's wort, Valerian	Excessive sedation, delayed emergence from anaesthesia
Opioid –analgesics	Valerian, Ginseng, St. John's wort	Additive CNS depression Reduced analgesic effectiveness
Antidepressants	St John's wort, Ginkgo	May increase serotonin levels. May lead to serotonin syndrome with other serotonergic agents
Antidiabetic agents	Garlic, Ginseng, Milkthistle, Damiana, Eucalyptus, Fenugreek, St. John's wort	May cause hypoglycaemia
	Ephedra, Licorice	May cause hyperglycaemia
Anticonvulsants	Ginkgo, Ephedra, Evening primrose oil	May increase risk of seizures, decrease drug effect
Antihypertensives	Ephedra, Devil's Claw, Guarana (caffeine), Licorice, Ginseng	May cause hypertension
	St. John's wort	Reduced effectiveness of some anti-hypertensives
Benzodiazepines	Valerian, Kava, Hawthorn, Hops St. John's wort	Excessive sedation Reduced effectiveness
Corticosteroids	Echinacea (<8wks use), Licorice	Immunostimulant effect of herb may offset immunosuppressant effect of corticosteroids.
	Echinacea (>8wks use)	May potentiate effect of immunosuppressant.
Immunosuppressants	Echinacea, Licorice	Immunostimulant effect of herb may offset immunosuppressant effects.
	St. John's wort	May reduce immunosuppressant levels
Digoxin	Licorice, Cascara, Senna, Aloe, Cassia	May cause hypokalemia (patient more vulnerable to digoxin toxicity)
	Ginseng	May cause falsely elevated digoxin levels
	St. John's wort	Decreases digoxin levels
Diuretics	Ginseng, Licorice	Decreases diuretic effects
Warfarin/anti-platelets/ anticoagulants	Feverfew, Ginger, Ginkgo, Garlic, Saw palmetto, Guarana, Passiflora, Cat's claw, Cranberry, Evening primrose oil, Dandelion, Bilberry, Boldo	May increase anticoagulant effects of warfarin
	Ginseng, Green tea, St. John's wort, Chamomile	May decrease anticoagulant effect of warfarin

HIV medication	Garlic, St John's wort, Milkthistle, Gingko Ginseng, Echinacea - use only short-term	May decrease protease inhibitor concentrations, increase risk of antiretroviral resistance
NSAIDS	Garlic, Gingko, Feverfew	Increased risk of bleeding
Laxatives	Licorice, Senna, Cascara	Increased risk of hypokalaemia
Oral Contraceptives	Licorice	Increased risk of fluid retention, hypertension
	Ginseng	Additive estrogenic effects
Proton-pump inhibitors	Cranberry, Gingko, St John's wort	Reduced effectiveness of PPIs
Antibiotics	Dandelion, Fennel	Decreased effectiveness of Fluoroquinolones
	Cinnamon	Decreased effectiveness of Tetracyclines Increased risk of phototoxicity with tetracyclines
	St John's wort	

weeks to develop fully, enzyme inhibition can occur within 2-3 days resulting in a rapid development of toxicity.⁹ Licorice decreases the metabolism of corticosteroids, leading to adverse and toxic effects from the build-up of corticosteroids.^{1,9,11}

Evidence obtained in vitro suggests that echinacea and chamomile may inhibit the cytochrome P450, isoenzyme CYP3A4. Concurrent use with drugs like alprazolam, simvastatin, calcium-channel blockers, and protease inhibitors could potentially increase serum drug levels and adverse effects.⁶⁻¹¹

Excretion

Changes in excretion may also affect serum drug levels. Herbal diuretics are quite weak and unlikely to cause large problems.⁵ However, chronic ingestion of licorice may result in hypokalemia and water retention and accordingly may interfere with various medications including antihypertensive and antiarrhythmic agents.^{7,8}

Pharmacodynamic Interactions

Additive interactions

A herb might produce the same kind of effect as the drug and give an increase in the drug effect (without increasing the amount of the drug).^{5,8,9} Therefore herbal sedatives, anticoagulants, antihypertensives and others may possibly increase the effect of a concurrent conventional drug taken for the same purpose. For example, the hypnotic activity of benzodiazepines is increased by valerian, and the anticoagulant action of warfarin is enhanced by gingko, garlic and ginger.^{1,5,8-11}

St John's Wort together with other serotonergic drugs e.g. SSRIs may produce the additive effect of the serotonin syndrome characterised by altered mental status, autonomic dysfunction and neuromuscular abnormalities.⁹

Antagonistic interactions

A herb might produce an effect that is contrary to the effect desired for the drug, thereby reducing the drug effect.^{5,8,9} Ephedra or caffeine-containing herbs (cola nut, guarana, mate, green tea), often used in combination for the additive cardiovascular effects in many herbal weight-loss products, may antagonize the effects of antihypertensive medications.^{5,8}

Conclusion

The fact that herbal medicines also have adverse effects and may give rise to potential drug-herb interactions does not imply that their use should be discouraged. Herbal medicines are not placebo and have been found to be efficacious,⁹⁻¹¹ sometimes being a suitable alternative to conventional drugs. Most herbal drugs have good safety profiles however, the fact that they are often taken over a long period of time in various drug cocktails, may provide the opportunity for enzyme induction/inhibition to take place⁵. The only fundamental issue is that they should be considered as medicines and their adverse effects and potential interactions considered.^{2,4,5-9} Health care providers need to look closely at the risks and benefits of herbal medicines, just as they do with conventional medicine.^{2,4,5-9} In order that this may occur it is important that pharmacists and doctors should be better informed on herbal medicines.^{2,8,9-11} Ideally more importance should be given in undergraduate course and Continuing Educational Programmes addressing herbal medicines should be offered to health professionals.^{2,4,8}

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Key points

- Pharmacists/doctors must take the initiative in creating opportunities to discuss herbal medicines with patients.^{2,4}
- Healthcare professionals must be aware of the dietary/multivitamin preparations which contain herbal medicines.
- Healthcare professionals must have access to reliable reference materials^{4,8-11} (Table 1) and utilise the Medicine Information Services at Mater Dei Hospital where a team of pharmacists are available to offer help on any enquiry including herbal/complementary medicine. (Contact number – 2545 6504).
- Pharmacists/doctors must be on the alert with regards to drugs having a narrow therapeutic window or where it is necessary to keep serum levels above a suitable level (e.g.anticoagulants, antidiabetic, antiepileptic, antihypertensive, anti-infective, immunosuppressants etc.)^{5,8,9}
- Pharmacies should only stock herbals from reputable manufacturers.^{2,4,5,9-11}
- Herbal medicines should be avoided in pregnancy/lactation and used with caution in patients with reduced liver/renal function.⁹⁻¹¹
- The stated dosage and duration of dosage should be adhered to.^{4,9-11}
- Patients should be advised to be alert to possible adverse effects and interactions with lab results.^{2,4,9-11}
- Herbal medicines should be stopped at least 7 days before surgery.⁹
- Patients should be advised not to take herbal medicines and conventional medications together or at the same time.^{4,8,9}

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Levitra® film-coated tablets and Levitra® orodispersible tablets (vardenafil) Prescribing Information (Refer to full Summary of product Characteristics (SmPC) before prescribing)

Presentation: Levitra® film-coated tablets: 5/10/20mg vardenafil (as hydrochloride trihydrate). Levitra® orodispersible tablets: 10mg (as hydrochloride). Indication: Treatment of erectile dysfunction. To be effective, sexual stimulation is required. Posology and method of administration: Film-coated: 10mg approximately 25–60 minutes before sexual activity. Based on efficacy and tolerability, dose may be increased to 20mg or decreased to 5mg. Maximum dose is 20mg/day. Can be taken with or without food. Onset of activity may be delayed if taken with a high fat meal. Orodispersible: 10mg approximately 60 minutes before sexual activity. Maximum dose is 10mg/day. It can be taken with or without food, but not with liquid. Elderly men: no dosage adjustment required, though increase to a maximum 20mg film-coated tablets dose should be carefully considered depending on individual tolerability. Children and adolescents: not indicated for individuals <18 years of age. Hepatic and renal impairment: Consider starting with 5mg film-coated tablets in patients with mild-moderate hepatic impairment or severe renal impairment. Orodispersible tablets should not be used in patients with moderate to severe hepatic impairment or with end-stage renal failure. Use with other medicinal products: In combination with CYP 3A4 inhibitors, the dose should not exceed 5mg film-coated tablets. Contra- indications: Hypersensitivity to vardenafil or to any excipients; co administration with

nitrate/nitric oxide donors (such as amyl nitrite); loss of vision in one eye due to NAION; men for whom sexual activity is inadvisable; severe hepatic impairment; end-stage renal disease requiring dialysis; hypotension; recent stroke or myocardial infarction; unstable angina; known hereditary retinal degenerative disorders; concomitant use of potent CYP3A4 inhibitors ketoconazole and itraconazole (oral form) in men older than 75 years; concomitant use of potent HIV protease inhibitors. Warnings and Precautions: Given cardiac risk associated with sexual activity, consider cardiovascular status. Vardenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Use with caution in patients with anatomical deformation of the penis or conditions which predispose to priapism. Combination with other treatments for erectile dysfunction is not recommended. Patients on alpha-blocker therapy: consider only if therapy is stable, initiate vardenafil at a starting dose of 5mg film-coated tablets and consider a time separation of dosing. Concomitant use with potent CYP 3A4 inhibitors should be avoided. A dose of 5mg film-coated tablets must not be exceeded when given concomitantly with erythromycin or clarithromycin. Avoid grape fruit or grape fruit juice. Prolongation of QTc interval-avoid use in patients with relevant risk factors. In case of sudden visual defect, treatment should be stopped. Administration to patients with bleeding disorders or active peptic ulceration should be considered carefully. Orodispersible tablets contain aspartame and sorbitol. Interactions: CYP3A4 inhibitors may reduce vardenafil clearance. Pregnancy and lactation: not indicated for use in women. Effects on ability to drive and use machines: patients should be aware of how they react to

Levitra® before driving or operating machinery. Undesirable Effects: Very common: flushing (film-coated tablets only) and headache. Common: nausea (film-coated tablets only), dizziness, nasal congestion, and dyspepsia. Serious side effects: cf. CI/ Warnings and Precautions-in addition: tachycardia, palpitations, angina pectoris, myocardial infarction, seizure, priapism, NAION, visual defect, laryngeal oedema, increased intraocular pressure, and sudden deafness. Serious cardiovascular events, including cerebrovascular haemorrhage, sudden cardiac death, transient ischaemic attack, unstable angina and ventricular arrhythmia reported post marketing in temporal association with another medicinal product in the same class. In addition, myocardial ischaemia and laryngeal oedema (film-coated tablets only) and paraesthesia/dysaesthesia, ventricular tachyarrhythmias and chest pain (orodispersible tablets only). Prescribers should consult the SmPC in relation to other side effects. Overdose: an increase in undesirable effects may be observed. Legal Category: POM. Package Quantities: Film-coated: 4x5mg, , 4x 10mg, 4x20mg. Orodispersible: 4x10mg. MA Number(s): EU/1/03/248/001-015. Further information available from: Bayer Health Care; c/o Alfred Gera & Sons Ltd, Triq il-Masgar Qormi, Malta. Tel. +356 21446205.

References:

1. Sperling H, Debruyne F, Boermans A, et al. *J Sex Med* 2010; 7: 1497–1507.
2. Levitra® ODT Summary of Product Characteristics. March 2008.
3. Heinig R, Weimann B, Dietrich H, et al. *Clin Drug Investig* 2011; 31(1): 27–41.

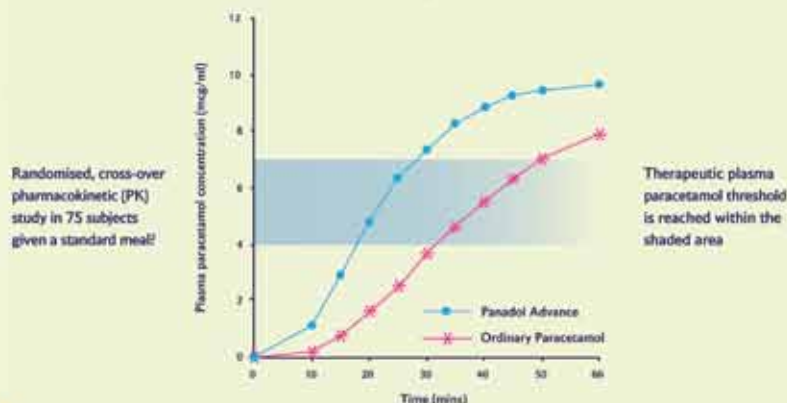
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Introducing New Panadol Advance 500 mg Tablets, the only paracetamol formulation to contain the unique Optizorb™ disintegration system.

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Product information. Panadol Advance 500mg film coated Tablets (paracetamol). Contains disintegrant system to accelerate dissolution. **Uses:** Mild analgesic and antipyretic. **Dosage and administration:** Adults and children: 12 years and over: Two tablets at ≥ 4 hour intervals. Max. 8 tablets in 24 hours. Children 6-12 years: Half to one tablet at ≥ 4 hour intervals. Max. 4 tablets in 24 hours. Do not use for >3days without doctors advice. Children under 6 years: Not recommended.

Contraindications: Hypersensitivity.

Precautions: Severe renal/hepatic impairment, non-cirrhotic alcoholic liver disease. Concomitant use of warfarin/other coumarin anticoagulants,

domperidone, metoclopramide, colestyramine. Refer to doctor if persistent headache or non-serious arthritis requiring daily analgesia. **Pregnancy/breastfeeding:** Pregnancy: Refer to doctor. Breastfeeding: not contraindicated. **Side effects:** Hypersensitivity including skin rash, blood dyscrasias. **Overdosage:** Immediate medical advice due to risk of delayed, serious liver damage. **Legal category:** OTC. **Product licence number:** AA450/00701. **Product licence holder:** GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K. **Package quantity:** Compact 12's. **Date of last revision:** November 2008. Panadol is a trade mark of the GlaxoSmithKline group of companies.



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