Practicing in the best interest of the patient
Editorial 3

Counterfeit medicines
Maria Cordina 4

Medicines and the internet
Segundo Mariz 8

Pharmacy practice in a European perspective
Th(Dick) F.J. Tromp, Kirsten Holme Christensen 11

Photosensitivity: light, sun and pharmacy
Mark L. Zammit 12

Sun and sea in summer
Victor Grech 18

Causes of cough
Lorna Marie West 23

Pain management in palliative care - choice of analgesia
Helen McClay 28

Aspects of HIV infection and treatment
Daniela Mallia 32
A different treatment approach for major depressive episodes

Symptoms of low motivation and energy in patients with major depression have been associated with noradrenaline and dopamine dysfunction. Now there is an alternative: Wellbutrin XR, a dual acting antidepressant, providing both Noradrenaline and Dopamine Re-uptake Inhibition (NDRI).

References
Practicing in the best interest of the patient

Maria Cordina BPharm(Hons), PhD(QUB)

Editor
Email: president@mcppnet.org

Practicing in the best interest of the patient requires one to always engage in practices which are ethical, professional and conducive to positive outcomes for the patient.

This edition of the journal opens with two papers addressing the issue of counterfeit medicines. The first paper gives an overview of the problem whilst the second specifically focuses on the availability of counterfeit medicines through the internet. These papers highlight the threat to patient safety which is of paramount importance. In addition, however, this phenomenon is attacking the most basic and fundamental function of the pharmacy profession, that of supplying safe and effective medicines to the public, especially when counterfeit infiltrate the legal supply chain. In our country medicines are only available through pharmacies. This is meant to provide patients with a safety net in terms of the quality of medicines available. It also provides the prescriber with the same guarantees. It is therefore of significant concern when prescribers and other health care professionals encourage patients to obtain their medicines outside the legitimate supply chain citing reasons related to the price or availability of medicines. When engaging in such practices, health care professionals are endangering patient’s health in addition to undermining national and global efforts to combat this problem. Healthcare professionals should be part of the solution and actively engage in educating the public on the dangers involved in such practices.

The papers by Zammit and Grech address health issues which are highly relevant to the summer months. While Zammit provides us with a comprehensive paper on photosensitivity incorporating phototoxicity and photoallergy, Grech gives an overview of common ailments encountered mainly in the summer months together with their management.

Cough is very often dismissed as just an annoying symptom and one that can be managed using basic over the counter preparations. West, provides evidence to dispel this notion and identifies various causes of cough which range from the trivial to the very serious. In practice these factors need to be taken into consideration as part of the management of this common presenting complaint.

The paper addressing the management of pain in palliative care by McClay primarily provides an overview of common analgesia used in the management of cancer pain highlighting their place in therapy.

Mallia discusses anti-retroviral therapy in the treatment of HIV in a highly informative and practical manner. This paper enables readers to become better acquainted with the various drugs used in the management of HIV.

The papers in this edition of the journal are diverse raging from those with a regulatory aspect, to topical issues and clinically oriented papers mirroring the evolving educational and practice needs.
Counterfeit medicines

Maria Cordina BPharm(Hons), PhD(QUB)
Senior Lecturer, Department of Pharmacy, University of Malta, Msida, Malta
President, Malta College of Pharmacy Practice
Email: maria.cordina@um.edu.mt

Educational aims
- To increase awareness regarding counterfeit medicines
- To highlight the threat to patient safety
- To dispel common misconceptions
- To encourage health care professionals to participate in medicines regulation

Key words
counterfeit medicines, patient safety, burden of counterfeit medicines

The issue of counterfeit medicines was mainly associated with developing countries, however it has now become of significant concern world-wide. While the exact extent of the problem is still unknown, the prevalence of counterfeit medicines is increasing, with a shift in focus from life style medicines to life saving medicines. As compared to 2005 the EU registered an increase of 380% of counterfeit medicines seized at EU borders in 2007.¹

Introduction
Within the European Union counterfeiting of medicines has been identified as a significant concern for patient safety, for industry and for policy makers both at EU level and at national level.² While counterfeit medicines have been around for some time, the original approach to dealing with this problem was to do so in a subtle manner so as not to undermine the patient's confidence in medicines and not to cause any unnecessary harm to legitimate business.³ The approach has now changed and all stake holders are urged to become involved and give their contribution to managing and containing this global problem. Consumers and public interest groups are encouraged to participate in medicine regulation.⁴

Defining the problem
Counterfeit medicines have been defined as ‘medicines which are deliberately and fraudulently mislabelled with respect to their identity and/or source. Counterfeiting can apply both to branded and generic products and counterfeit products may include products with the correct ingredients or the wrong ingredients, without active ingredients or with insufficient active ingredient or with fake packaging’.⁵

Counterfeit medicines are not just substandard medicines, where in the latter case there are problems with the manufacturing process by a known manufacturer. Counterfeit medicines are made by (unknown) people with the intention to deceive and who have no regard whatsoever for patient health and safety. Engaging in the counterfeiting of medicines has the potential for making enormous profits and counterfeiters have the possibility of quickly adapting and adjusting to different situations and products to maximise their profits.⁶

Over recent years there has been a sharp increase in counterfeit medicines seized by customs at EU borders. It is estimated that in industrialised countries counterfeit medicines have a market share of 1%.⁷ As evidenced by reports from various national drug agencies, initially counterfeiters targeted lifestyle medicines such as erectile dysfunction and anti-obesity drugs, however they have now shifted their focus to lifesaving drugs such as those used in the treatment of cardiovascular disease, infections and cancers to mention a few.⁸,⁹

Apart from using the internet, counterfeiters are also now targeting the licensed distribution chain including wholesalers and pharmacies as this gives them the ability to deal in large volumes of distribution of medicine.

The legitimate distribution chain is a rather complex one and offers counterfeiters a good opportunity to infiltrate the system. Once a counterfeit product has entered the legitimate system, it becomes rather difficult to detect. When considering the EU, counterfeit medicines are usually produced outside the EU and then ‘imported for export’, i.e. when these products are allegedly not placed on the market in the EU but enter customs territory under transit rules and undergo further minor processing. While they should not be made available within the EU, these medicines can be redirected and enter the legal distribution chain. As in the case with Malta, where to date no cases of counterfeits were found and reported in the legal supply chain, counterfeit drugs are often detected in T1 transit, such as in customs territory where non-EU goods are stored and handled.³
Table 1. What encourages counterfeiting of medicines?7

- Medicines attractive for counterfeiting
- Lack of political will and commitment to establish a strong national medicines authority
- Lack of appropriate medicine legislation
- Absence of, or weak national medicines regulatory agency
- Weak enforcement including corruption and conflict of interest
- Shortage or erratic supply of medicines
- Inappropriate use of medicines
- Price differentials
- Inefficient co-operation between stake holders
- Lack of control over export medicines
- Trade through several intermediaries
- Trade through free-trade zones/free ports

Misconceptions a regarding counterfeit medicines

One of the main misconceptions is that counterfeiting of medicines is a problem which only affects developing countries. While the areas which are the most affected are indeed developing countries, Europe and the rest of the industrialised world is increasingly being targeted as can be seen in Table 2. In developing countries antibiotics and anti-protozoals such as anti-malarial medicines are commonly counterfeited while in developed countries hormones and steroids account for the majority of the cases reported.7

Table 2. Reported cases of counterfeit medicines7,4,10

**UK**
- Cialis 20mg
- Reductil 15mg
- Lipitor 20mg
- Zyprexa 10mg
- Plavix 75mg
- Casodex 50mg
- Seretide 250
- Evohaler 8ml pressurised inhalers
- Sensodyne original
- Sensodyne Mint 50ml tubes

**USA**
- Xenical
- Alli

**United Republic of Tanzania**
- Metakelfin (anti-malarial)

**China**
- Anti-diabetic traditional medicine

It is commonly thought that these are harmless copies or concern issues not affecting the health of the patient but just intellectual property since it is erroneously assumed that only branded products are targeted. As can be seen from the definition, this is not the case as both generics and branded products may be targeted for counterfeiting. Counterfeiters target medicines that can provide them with the largest profit and lucrative markets i.e. high consumption and expensive medicines are main targets.

Another misconception is that it is easy to tell the difference between a counterfeit medicine and an authentic medicine. This is not the case at all. With the technology currently available counterfeiters are able to make their product nearly identical to the original both in the case of the appearance of the medicine itself as well as the packaging. It often requires laboratory analysis to determine if a product is counterfeit.

**Threat to patient safety**

The threat to patient safety is significant. Counterfeit medicines could possibly not contain the correct active ingredient or contain the correct active ingredient in sub-therapeutic quantities alternatively they may contain toxic materials which result in the patient being poisoned.

In 2009 during the Influenza A (H1N1) pandemic significantly more reports were registered regarding the increased occurrence of counterfeit medicines. Counterfeiters identified this as a window of opportunity to sell fraudulent, adulterated or unauthorized antiviral medication or vaccines, via the Internet.11

Currently the over-the-counter anti-obesity drug, Alli®, has been targeted by counterfeiters and is available over the internet. The FDA has warned that instead of the registered active ingredient orlistat, the preparation contains sibutramine, with patients taking up to twice the recommended maximum dose of the latter drug if they are following dosing instructions for Alli®. When taken in excess, sibutramine can lead to elevated blood pressure, stroke and cardiac arrest in persons with a history of cardiovascular disease and healthy individuals can experience anxiety, nausea, palpitations, insomnia and slight increase in blood pressure.22

The case of counterfeit anti-diabetic traditional medicine reported in China found the preparations to contain six times the normal dose of glibenclamide which leads to the death of two individuals and hospitalization of nine people.7

A number of cases have been documented within EU member states. A document published in 2008 provides examples of cases reported during 2006/2007. A seizure of counterfeit heparin (Belgium/Germany) was found to contain a heparin like contaminant which was added to heparin resulting in allergic reactions and possibly caused deaths in 81 cases and side-effects in hundreds of patients.1

This document also lists Malta as having ‘various’ counterfeit cases of hundreds of packs relating to several diseases.1

As clearly demonstrated, the use of counterfeit medicines may result in therapeutic failure leading to increased morbidity and possibly mortality, which not only translates into a negative effect on the patient’s health and quality of life but also leads to additional medical interventions, prolonged hospital stays, additional costs for treatment translating into an increased burden on the national health care service, on the patient and carers.

Unless an effective means of addressing this problem is found, once counterfeit medicines enter the legal supply chain, estimates indicate that they will be a significant burden to the EU as indicated by the following estimates: 1

**Main costs - direct costs**

- Costs of hospitalisations as a consequence of treatment using counterfeit medicines: Projected base line until 2020 of avoidable hospital admissions is
estimated to cost the EU between 1.8bn EUR-22bn EUR

- Costs occurring in an ambulatory setting for treating the consequences of a treatment involving counterfeit medicines:

Projected base line until 2020 of avoidable medical treatment at community level by primary health care doctors is estimated to cost the EU between 93m EUR and 93bn EUR.

Main costs - indirect costs

Using Quality Adjusted Life Years (QUALYs), which combine effects on life expectancy and quality of life within a single measure, with 1 QUALY being equal to one year of life expectancy in full health, the projected base line cost until 2020 is expected to lay between 7.65bn EUR and 93bn EUR.

Combating counterfeit medicines

All stake holders are encouraged to actively participate in combating counterfeit medicines. Patients, who are usually the first to notice something wrong with their medicine e.g. different taste, unusual colour, novel side-effects when compared to their regular medicines, are encouraged to make a report. Pharmacists are expected to be aware and vigilant, purchasing their medicines only from a reputable source. The publication entitled ‘Counterfeit medicines: Advice for health care professionals’ provides an excellent guide for pharmacists.12 Medical doctors are strongly advised not to encourage patients to obtain their medicines outside the legitimate supply chain, which in Malta, are only licensed pharmacies.

At a global level The World Health Organisation set up the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) which is comprised of international organizations, non-governmental organizations, enforcement agencies, pharmaceutical manufacturers associations and drug and regulatory authorities. Its aim is to halt the production, trading and selling of fake medicines around the globe.11

At a national level Malta is actively participating in the Council of Europe Working group on the Pharma package where one of its’ pillars is the topic of counterfeit medicines. This group’s aim in the Pharma-package pillar is to submit a proposal for a Directive of the European Parliament and of the Council amending Directive 2001/83/EC with regards to the prevention of entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source. Once approved by the EU parliament this directive amending directive 2001/83 will be transposed into national legislation leading to all EU member states having harmonised legislation with regards to counterfeit medicines.14

Conclusion

It is essential that healthcare professionals be well informed regarding the significant threats posed by the availability of counterfeit medicines. In their practice they should seek to educate the general public about the matter and in addition should never encourage patients to obtain their medicines in a way which could jeopardise their health and well being.

Key points

- Counterfeit medicines are medicines that are deliberately and fraudulently mislabelled with respect to identity and/or source
- Use of counterfeit medicines can result in treatment failure or even death
- Erosion of public confidence in health-delivery systems may result following use and/or detection of counterfeit medicines
- Both branded and generic products are subject to counterfeiting
- Patients should never be encouraged to obtain medicines outside the legitimate supply chain

References


Medicines and the internet

Segundo Maríz MD
Senior Medical Assessor, Medicines and Healthcare products Regulatory Agency, Market Towers 1 Nine Elms Lane, London, SW8 5NQ UK
Email: segundo.mariz@mhra.gsi.gov.uk, segundomariz@hotmail.com

Educational aims

• To create awareness amongst health care professionals of benefits and risks associated with the internet pharmacy.
• To highlight the dangers associated with purchasing counterfeit medicines via an internet pharmacy.
• To increase healthcare professionals awareness in order to reduce the potential risks to public health.

Keywords
rogue internet pharmacy, regulatory, counterfeit, patient

The internet has been a major revolution in enhancing the accessibility of information and goods to the public challenging well-established healthcare practices. The Internet Pharmacy is now an integral part of these searches giving enhanced access to medicines to the public. It has become a global multibillion dollar market and brings with it threats and opportunities which could not have been foreseen. A Rogue Internet Pharmacy is a very real threat to the patient and healthcare professional. Of serious concern is the increase in distribution of counterfeit medicines through these sites. The EU is currently preparing legislation to regulate Internet Pharmacy Services to protect patients.

Introduction

The internet has become a major tool to empower patients since it became freely accessible to the public in 1997. Accessing medical information is one of the most common reasons for people to use the web. In addition a new e-commerce market has been created which has revolutionized the public's access to goods globally.¹

The internet pharmacy is a perfect example of the impact of increased access to healthcare goods offered by the newly created e-commerce market. Online pharmaceutical sales in the US alone, for example have grown from around 1% of the US pharmaceutical market to around 4% in 2007. A prime and vulnerable patient population, the elderly, use it extensively in the US to shop for cheaper prescription medicines where savings of up to 30% can be made.² Many do so confidently that their purchases offer the same quality and guarantees as those medicines bought in the pharmacy.³

The number of online pharmacies have expanded exponentially in the last 13yrs. Services and fees are often associated which are not currently effectively regulated. Of concern are the cyberdoctor and the source of the medicines sold.⁴,⁵

In Europe initial moves attempted to restrict or prohibit the movement of medicines between nations via online or Internet pharmacies. (DocMorris case: Case C-322/01 Deutzer Apothekerverband eV v 0800 DocMorris NV – 11 December 2003)⁶ European Union Treaties, Regulations and Directives have changed the capabilities of national professional associations to challenge the restrictions of internet sales of medicines within the Europe Union but not from third parties outside of the Union. European Union treaties provide a legal framework for e-commerce thereby providing the freedom of movement of medicines.⁵,⁶ The variability regarding national legislation, licensing, pricing and reimbursement has rendered the applicability of this treaty more complex and open to legal challenge particularly regarding prescription only medicines.⁶

Patients wish to have access to cheaper medicines or medicines which are more difficult to obtain in their nation state because of the national legislation or simply because of lack of accessibility.

The Internet pharmacy offers them the possibility to do this across borders.⁷,⁸,⁹ This new enhanced accessibility presents serious challenges to well-established healthcare practice which contains benefits and threats.¹⁰

Types of internet pharmacies and their services

Internet Pharmacies can be classified broadly into 4 types:¹

1. Extensions of pharmacy chains that offer a variety of online health information and products
2. Independent pharmacies, which often use the Internet to try to compete with larger chains
3. Mail-order pharmacies that use the Internet to facilitate the ordering process
4. Pharmacies that operate exclusively online.

Benefits associated with this service are linked with the ease, convenience and increased choice offered by a 24hr service open 7 days a week where comparisons can be made between a wide range of products. Increased access to consumer information and information exchange with the service provider which offers the potential for patients to enquire about their conditions and what therapeutic options maybe available to them. This is generally done anonymously and within a framework of privacy. Finally the financial savings can be considerable particularly in certain countries such as the United States.

Current concerns with the internet pharmacy

Currently a harmonized global regulation of these services does not exist. In the absence of appropriate harmonized laws, treaties and cooperative agreements between nation states, online sellers can evade regulation in certain jurisdiction by engaging in regulatory arbitrage (i.e. operating websites in a jurisdiction which has the least restrictive regulatory framework).

In many instances those evading regulation do so in order to engage in illegal activities. These are “Rogue Internet Pharmacies” which are involved in various illegal acts such as selling prescription drugs without a valid prescription, selling counterfeit or poor quality drugs, and providing online medical consultations (cyberdoctor) for prescribing and dispensing drugs. These “Rogue Internet Pharmacies” present a great danger to the public due to the potential harm, which can be caused by their illegal activities.
Challenge to traditional healthcare practice

With patients directly accessing online healthcare services like the Internet Pharmacy the traditional safeguards assured by the patients physician and the dispensing pharmacist are by-passed. The patient as a result confides anonymously to a cyberdoctor who often does not know the patients current condition (in some cases this is just a questionnaire service which directs a patient to a treatment also offered by the online pharmacy). As a consequence the patient is no longer protected and becomes a consumer who is exposed to services whose aim is not to a service in the interests of public health but to obtain financial gain.4

The cyberdoctor is troubling in that the patient-doctor/patient-pharmacist relationship is threatened but when linked to the distribution of prescription only medicines this can be extremely harmful.5,6 In particular the risk of counterfeit medicines is perhaps the greatest.5-7 Counterfeit medicines have progressively infiltrated the distribution chain through the Internet pharmacy.7,8 Many medicines are now manufactured in areas outside the traditional sites in the Developed World. Regulatory control is less effective and the quality of medicines more variable with counterfeit medicines being the worst end product of a now weakened system of quality control. Online pharmacies are often difficult to trace making the establishment of the Rogue Internet Pharmacy easier.9,10 These sites often work from an unregulated site, have no address, are registered in China and hosted in Russia. The WHO estimates that 50% of medicines available to consumers from Internet sites which conceal their physical address are counterfeit. The internet offers them the possibility to target the wealthiest markets where connectivity is greatest; Europe and North America. This represents a direct challenge to traditional pharmacies which dispense and ensure the quality of prescription only medicines.

In the UK over the last few years there have been several serious cases of these sites distributing these drugs within the country or using the country as a warehousing transit point for other markets for example in the North America. Originally, these involved life style drugs but recently these have started to include life-saving drugs. Some of the high profile cases are reported on the UK MHRA (Medicines and Healthcare Products Regulatory Agency) website.10

Current actions to address the threat

Governments Agencies are increasingly installing surveillance systems to monitor for the presence of Rogue Online Pharmacies. With these systems for example the MHRA recently conducted a large operation to seize counterfeit drugs distributed through Internet Pharmacies. These approaches however are not preventative.

In the US the FDA has made efforts to set up a system of accreditation of these services so that consumer and healthcare workers can be protected and be guaranteed that a regulatory framework is in place to ensure that the quality of the service is to an adequate standard.

In the EU efforts are current on-going to draft and approve legislation which will effectively regulate and clarify the penalties imposed on those in breech of the new legislation (Euractiv 28 April 2010 Parliament takes aim at illegal online pharmacies). Indeed in July 2010 the European Parliament will have a plenary session to discuss the Falsified Medicines Directive.8

Conclusion

The advent of the internet and its enhanced accessibility has opened a new era of e-commerce which offers benefits and risks. The Internet Pharmacy is a case in point. The services are often but not always associated with a credible wholesale source of pharmaceutical products.

With the development of the global internet the accessibility of markets from different parts of the globe has led to a situation of regulatory arbitrage. This means that certain countries have weaker regulatory frameworks from which Rogue Internet Pharmacies can operate and access with impunity the richer markets of Europe and North America or distribute cheap counterfeit medications to poor countries. This leads to a breakdown in the traditional mechanisms of regulation of healthcare services involved in the dispensing of prescription medicines where there is a relationship between patient, physician and pharmacist. The patient becomes a consumer and is no longer protected by the healthcare professionals who are often not aware of their purchases on the internet.

Efforts are currently on going in the European Parliament to endorse a new EU Directive to improve the regulation of this online service and penalize rogue internet pharmacies.

Key points

- Various types of internet pharmacies exist, not all of which are engaged in illegal activity
- Rogue Internet Pharmacies involved in illegal activities e.g. selling prescription drugs without a valid prescription, selling counterfeit or poor quality drugs, and providing online medical consultations (cyberdoctor) for prescribing and dispensing drugs
- Online pharmacies are often difficult to trace making the establishment of the Rogue Internet Pharmacy easier
- WHO estimates that in over 50% of cases, medicines purchased over the Internet from illegal sites that conceal their physical address are counterfeit
- EU working on legislation to combat counterfeit medicines

References


Issue 16 Summer 2010 Journal of the Malta College of Pharmacy Practice 9
Atorvastatin

10mg, 20mg, 40mg tablets

Lipid Reducing Agent

**Composition:** Each tablet contains Atorvastatin calcium equivalent to Atorvastatin.

**Therapeutic indication:** Atorvastatin is used as a supplement to a change in diet for reduction of elevated total cholesterol, LDL cholesterol, triglycerides, in the treatment of patients with primary hypercholesterolemia, homocysteinuria, familial hypercholesterolemia, or combined hyperlipidemia to achieve and maintain target levels of serum cholesterol and triglycerides. It is also used in the treatment of patients with certain forms of familial hypercholesterolemia who have not responded to diet and who require additional reduction in serum cholesterol and triglycerides. Atorvastatin may also be used in the prevention of coronary heart disease in patients at risk for its development.

**Description:** Atorvastatin is a synthetic drug derived from a subclass of a new class of drugs called HMG-CoA reductase inhibitors (statins). It reduces cholesterol by inhibiting the production of cholesterol in the liver. Atorvastatin should be taken once a day, usually at bedtime. The dose should be increased in the presence of hypolipidemic effects.

**Contraindications:** Atorvastatin should be used with caution in patients with liver disease or a history of liver disease. Atorvastatin is contraindicated in patients with active liver disease and in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

**Side effects:** Common side effects of Atorvastatin include muscle pain, nausea, and stomach discomfort. Rare side effects include liver function test abnormalities, myalgias, and rhabdomyolysis.

**Precautions:** Patients with diabetes, renal impairment, and liver disease should be monitored closely. Atorvastatin should be used with caution in patients with history of myopathy. Patients should be advised to report any muscle aches or weakness.

**Dosage and administration:** The starting dose is 10 mg daily. The dose may be increased to 20 mg daily or 40 mg daily in patients who require a greater reduction in cholesterol levels. The dose should be increased in patients with severe hypercholesterolemia or with history of atherosclerotic disease.

**Pharmacological effects:** Atorvastatin reduces plasma levels of total cholesterol, LDL cholesterol, and triglycerides. It also increases plasma levels of HDL cholesterol.

**Clinical studies:** Clinical studies have shown that Atorvastatin significantly reduces the risk of coronary heart disease in patients with hypercholesterolemia.

**Advantages:** Atorvastatin is well tolerated and has a favorable side effect profile compared to other statins.

**Disadvantages:** Atorvastatin can cause muscle pain, nausea, and stomach discomfort. It may also cause liver function test abnormalities.

**References:**


**Marketing Authorization Holder:** AECIS Ltd.

**For full prescribing information, contact the local representative of the Marketing Authorization Holder.
Pharmacy practice in a European perspective

Th(Dick) F.J. Tromp PhD
President, EuroPharm Forum WHO Collaborating Center Milnersvg 42, Hillerod, Denmark
Email: secretariat@europharmforum.org

Kirsten Holme Christensen MSc(Pharm)
Professional Secretary, EuroPharm Forum WHO Collaborating Center Milnersvg 42, Hillerod, Denmark
Email: euro@europharmforum.org

In 1992 European pharmacy organisations joined in the EuroPharm forum. This network has for the last two decades focused on development of pharmacy practice. Today 30 associations from 22 countries are members of the Forum.

The mission of the EuroPharm Forum is to improve health in Europe according to priorities set by the WHO. A very close relationship to WHO Europe is therefore essential to the EuroPharm Forum.

Many member countries have contributed to the professional work, to the benefit of all members. In the beginning, there was a need for guidelines to pharmacy practice work, and the work of the EuroPharm Forum - e.g. on asthma, smoking and diabetes - was well accepted and used as a basis for national work in many member countries. Another important aspect of the EuroPharm Forum work was the twinning projects where more developed countries twinned with countries with emerging health systems in order to improve pharmacy practice. WHO Europe funded part of the work while the remaining funding came mainly from the developed countries.

Today the activities of the Forum match the development and wide variety of members' situation. The latest initiative is a knowledge and search facility for pharmacy practice development. The Observatory is a webpage, www.europharm.pbworks.com, where pharmacy practice-interested people can start discussions and search for relevant pharmacy practice papers. The aim is to constantly develop and expand a site where all pharmacy practice materials can be found and discussed. The Observatory is located on a public homepage and welcomes all relevant contributions.

Since 2002 the EuroPharm Forum has collected information about pharmacy practice activities among its members. This information is published each year in the Country Database. Data from the database is used to inspire, make contracts and exchange experiences. The Country Database is located on a members-only webpage.

As mentioned above, the core activity of the Forum was in the past to develop tools like model programmes, reports, guidelines, analyses, etc. The latest activities in this area have been a study carried out by the EuroPharm Forum Working Group Pandemic Influenza which resulted in the report: "The Role of the Pharmacist in Fourteen National Pandemic Influenza Preparedness Plans in Europe; an Analysis", which was released a few months before the pandemic influenza exploded. A guide prepared by the EuroPharm Forum Working Group on Quality of Medicines resulted in a "Framework for a Guide on counterfeit medicines for pharmacists", and latest the EuroPharm Forum supported the work of the Hungarian National Committee of Pharmaceutical Care on a "Metabolic Syndrome Pharmaceutical Care Programme". All materials can be found on the EuroPharm Forum website.

An important part of the EuroPharm Forum’s work is to support the implementation of pharmacy practice activities. The cd-rom toolbox is an interactive education tool providing a step-by-step approach to developing national implementation plans for professional programmes. Generalised from the EuroPharm Forum pharmacy-based service programmes, the cd-rom has been designed to stimulate and support practising pharmacists, health professionals, universities and pharmacy schools as they disseminate and implement best practices in any type of public health services.

The cd-rom toolbox collates all the EuroPharm Forum model programmes and includes four central elements, i.e. a fictive case study, a real case study, the Forum guidelines and instruments, and country materials. The toolbox is mainly designed for practising pharmacists, decision-makers and pharmacy group managers, but is applicable for any practising health professional.

Almost every year EuroPharm Forum conducts one or two conferences. The subjects of the conferences are rooted in the professional agenda of the EuroPharm Forum at the time of the conference. This fall a conference on “The role of pharmacists in individual patient care” will take place in Copenhagen.

More information on the EuroPharm Forum can be found through the web pages. At the moment, the EuroPharm Forum hosts and maintains three web pages: the EuroPharm Forum homepage, www.europharmforum.org, the members-only Discussion Forum, and the Observatory. It is also possible to subscribe to the Newsflash which updates on the EuroPharm Forum business and pharmacy practice in general.
Photosensitivity: Light, sun and pharmacy

Mark L. Zammit  BPharm(Hons), MSc(Agr Vet Pharm), Pg Dip Med Tox(Cardiff), MSc Med Tox(Cardiff), MEAPCCT

Principal Pharmacist, Clinical Pharmacy and Medicines & Poisons Information, Pharmacy Department, Mater Dei Hospital, Malta
Email: mark.l.zammit@gov.mt

Introduction

Light has a profound effect on us. We may not be conscious enough as regards the existences of many phototoxic substances and chemicals. A phototoxic substance is a chemical compound which becomes toxic when exposed to light. Phototoxicity may be manifested in various ways. Proper use of sunscreens may play a vital role in the prevention of many such reactions.

Educational aims

• To provide an overview of different types of drug-induced photosensitivity reactions
• To provide an overview of treatment options and prevention strategies
• To provide a practical help as regards the use of sunscreens

Key words
phototoxic reactions, photoallergic reactions, photosensitivity reaction, sunscreen, sun protection factor

Photosensitivity and its epidemiology

In the context of pharmacy, an important effect of light is what is termed as photosensitivity. Drug-induced photosensitivity is termed as an undesirable pharmacological reaction in light irradiation.\(^5\) Exposure to either the chemical or the light alone is not sufficient to induce the disease; however, when photoactivation of the chemical occurs, one or more cutaneous manifestations may arise. These include mainly either a phototoxic or a photoallergic reactions, but may also include a planus lichenoides reaction, pseudoporphyria, subacute cutaneous purpura, erythematous as well as hyperpigmentation, pigmented changes or berloque dermatitis.

Photosensitivity reactions may result from systemic medications and topically applied compounds (Table 1).

Wavelengths within the UV-A (320-400 nm) range and, for certain compounds, within the visible range, are more likely to cause drug-induced photosensitivity reactions, although occasionally UV-B (290-320 nm) can also be responsible for such effects. UV-B wavelengths are most efficient at causing sunburn and nonmelanoma skin cancer.\(^6\)

Photosensitivity eruptions typically occur in locations with prominent sun exposure such as in the face, extensor extremities, upper chest and back of neck. Characteristic
Reactions are generally uncommon. Most common form, whereas photoallergic (Table 2). Phototoxic reactions represent the number of distinguishing characteristics photoallergic reactions. However, they have difficult to differentiate phototoxic from patients who present with photosensitivity, it is often mechanism. They are the result of either classified according to the underlying 

sites of sparing include the upper eyelids, below the nose and chin, behind the earlobes and the finger-webs. Photosensitivity reactions can be classified according to the underlying mechanism. They are the result of either phototoxicity or photoallergy. In patients who present with photosensitivity, it is often difficult to differentiate phototoxic from photoallergic reactions. However, they have a number of distinguishing characteristics (Table 2). Phototoxic reactions represent the most common form, whereas photoallergic reactions are generally uncommon.6,10

### Table 1. Some medications and other substances associated with photosensitivity

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Ciprofloxacin and other quinolones, sulfonamides, dapsone, griseofulvin. Tetracyclines [especially demeclocycline; less frequently doxycycline, oxytetracycline and tetracycline; minocycline rarely]</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Dimenhydrinate, cetirizine, loratidine</td>
</tr>
<tr>
<td>Anti-inflammatories [NSAIDS]</td>
<td>Ibuprofen, naproxen, piroxicam</td>
</tr>
<tr>
<td>Anti-malarials</td>
<td>Chloroquine and related compounds (such as hydroxychloroquine), Sulfadoxine with pyrimethamine [Fansidar®]</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>ACE inhibitors, amiodarone, amlodipine, clopidogrel, diltiazem, furosemide, losartan, nifedipine, statins, thiazide diuretics, sotalol</td>
</tr>
<tr>
<td>CNS agents</td>
<td>Carbamazepine, clomipramine, chlorpromazine, phenothiazines, tricyclic antidepressants, selegiline, zolpidem.</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Acetazolamide, oral contraceptives and oestrogen, chemotherapy agents, ranitidine, sulfonylureas, tacrolimus</td>
</tr>
<tr>
<td>Topical agents</td>
<td>Deodorants in soaps; perfumes; coal tar products</td>
</tr>
<tr>
<td>Plants and herbs</td>
<td>Celery, giant hogweed, angelica, parsnip, fennel, dill, anise, parsley, lime, lemon, rue, fig, mustard, scurf pea, and chrysanthemums</td>
</tr>
<tr>
<td>Essential Oils</td>
<td>Fig leaf absolute oil; taget oil; vergena oil and verbena absolute oil; bergamot oil; cumin oil; lime (expressed) oil; angelica root oil; rue oil; opoponax oil; orange (bitter expressed) oil; lemon (expressed) oil; grapefruit (expressed) oil</td>
</tr>
</tbody>
</table>

Note: This list is NOT comprehensive. Manufacturers’ package inserts should be consulted regarding potential photosensitivity of medications.

Photosensitivity reactions and resemble a severe sunburn.12 The skin damage that occurs in phototoxic reactions is typically confined to areas of exposed skin only. Occasionally the nails may also be affected. The phototoxic effect is a well-known phenomenon referred to as photoonycholysis.7,12 A classic example of a medicine associated with photosensitivity [sometimes also with photoallergy] is amiodarone, which induces photosensitivity in 10-50% of the patients treated with this drug.9

However some reports even mention rates as high as 75%.11 As mentioned beforehand the development of phototoxicity is dose-dependent. It is reported that an amiodarone-induced phototoxic reaction depends on a total dose of amiodarone of 40g which is the minimal cumulative dose requirement. Under the regimens commonly used, photosensitivity can be expected after 4 months of continuous amiodarone treatment and appears to be unrelated to the skin type. Phototoxicity gradually decreases and returns to normal between 4 and 12 months after the withdrawal of amiodarone.4 Photo-onycholysis, or separation of the distal nail plate from the nail bed, is another manifestation of phototoxicity. Photo-onycholysis has been reported with solar energy by acting as a chromophore, causing absorption of ultraviolet light and causing damage to the skin tissue.5

Acute phototoxicity often begins as an exaggerated sunburn reaction with erythema and oedema that occurs within minutes to hours of light exposure; vesicles and bullae may develop with severe reactions.9 The lesions often heal with hyperpigmentation, which resolves in a matter of weeks to months. Chronic phototoxicity may also appear as an exaggerated sunburn reaction. Lichenification often develops because of repeated rubbing and scratching of the photosensitive area.

Distinguishing phototoxic reactions from photoallergic reactions strictly based on physical appearance of the lesions may be difficult.6 In contrast to photoallergic reactions drug-induced phototoxic reactions typically occur on first exposure to the drug, and they are often dose-related.5,9,10 Cases of drug-induced phototoxic reactions are associated with a much quicker onset relative to cases of drug-induced photoallergy.12 This could typically be within 30 minutes to several hours after exposure to UV light. In general phototoxic reactions are less severe than photoallergic reactions and resemble a severe sunburn.12 The skin damage that occurs in phototoxic reactions is typically confined to areas of exposed skin only. Occasionally the nails may also be affected. The phototoxic effect site is a well-known phenomenon referred to as photoonycholysis.7,12

Phototoxic reactions may occur in almost any individual who received a high enough dose of the offending agent coupled with sufficient exposure to light irradiation.11 The occurrence of drug-induced phototoxicity reactions can thus be dependent on the concentration or amount of the sensitising agent and the amount of light exposure.11

**Phototoxic reactions**

Phototoxic reactions are non-immunologic in nature. In these reactions the drug, after ingestion or topical application is believed to potentiate the
Table 2. Differentiating characteristics of phototoxicity and photoallergy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phototoxicity</th>
<th>Photoallergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of occurrence</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Non-immune mediated</td>
<td>Immune mediated [Type IV]</td>
</tr>
<tr>
<td>Onset</td>
<td>Immediate (minute to hours)</td>
<td>May be delayed (hours to days)</td>
</tr>
<tr>
<td></td>
<td>after exposure to drug and sunlight</td>
<td>after exposure to drug and sunlight</td>
</tr>
<tr>
<td>Distribution</td>
<td>Usually confined to exposed skin</td>
<td>May affect unexposed skin</td>
</tr>
<tr>
<td>Potential for pigmentary changes</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Dose dependency</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Potential for cross-reactivity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential for persistent light reaction</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Exaggerated sunburn</td>
<td>Dermatitis</td>
</tr>
</tbody>
</table>

the use of many systemic medications, including tetracycline, chloramphenicol, fluoroquinolones, oral contraceptives and mercaptopurine. Photo-onycholysis may be the only manifestation of phototoxicity in individuals with heavily pigmented skin.4

**Photoallergic reactions**

Unlike phototoxic reactions drug-induced photoallergic reactions are the result of an immunologic response. The proposed mechanism of photoallergic reactions is type IV cell-mediated hypersensitivity response.5 It is postulated that when UV light reacts with either the drug or the drug’s metabolites in the skin; this induces a structural change in the drug so that it behaves as a hapten.5,10 This hapten combines with proteins in the skin to form a hapten-protein complex [a compete antigen]. On subsequent exposure to the drug a hypersensitivity response is elicited.10 Once the patient is sensitised to the drug only minimal amounts of drug exposure are subsequently required to produce a photoallergic reaction.5

Photoallergic reactions are thus the result of cell-mediated immunity and require an initial sensitization period – an acute, subacute or chronic eruption which is usually described as a papulovesicular, eczematous and intensely pruritic rash generally appears 24 hours or more after exposure [onset can be anywhere from 24 to 48 hours to up to 14 days after sun exposure] this due to the fact that photoallergic reactions involve the immune system and there is typically a delay between the time of exposure to the drug and the actual onset of the skin eruption.6,7,11 In general photoallergic reactions occurring in sensitised patients are not dose dependent.12 Generally photoallergic reactions involve mainly direct sun-exposed areas but in severe cases may also affect areas that are normally protected from UV light.4 Patients with photoallergic reactions should not take the offending drug again ever.

**Pigmentary changes and berloque dermatitis**

Other less common skin manifestations of phototoxicity include pigmentary changes. A blue-gray pigmentation is associated with several agents, including amiodarone, chlorpromazine, and some tricyclic antidepressants. Reactions to psoralen-containing botanicals (phytophotodermatitis) and drugs may resolve, with a brownish discoloration. Frequently, the pigmentary change is preceded by a typical sunburn reaction. If the reaction is not severe, some patients may not notice the erythema.

Pigmentary changes occur quite commonly as a manifestation of photosensitivity in patients receiving long-term high-dose amiodarone therapy.13-18 A blue-gray discoloration commonly develops on areas of skin that are subjected to unprotected light exposure due to deposition of amiodarone and its metabolites within the dermis.3-16,18 Amiodarone-related hyperpigmentation develops after an average of 20 months of continuous amiodarone treatment and a minimal total dose of 160g amiodarone in about 8% of the patients, mainly of skin Type 1 - porcelain white skin. [Type 1 always burns and never tans. This type skin has the highest risk of skin cancer and wrinkles more readily than other types. Most Type 1 skin owners will have red or pale blonde hair, be blue-eyed and have freckles].13-18

A specific form of hyperpigmentation is what is termed as berloque dermatitis. The clinical presentation of berloque dermatitis may be classically divided into two phases. The initial acute inflammatory phase consists of erythema, oedema, pain, pruritus, and increase in skin temperature around the area of contact with the phototoxic agent. The second stage is hyperpigmentation of the lesion with patients typically presenting with small areas of redness or pigmentation of the skin, usually on sun-exposed areas. A careful history may reveal use of a perfume or fragrance-containing product on the skin prior to a period of sun exposure, such as
FOR SMOKING CESSATION

THE POWER TO HELP THEM QUIT. FINALLY. 14

A new class of oral prescription therapy with a unique duel action: 12

- Partial agonist: Reduces craving and withdrawal symptoms 3
- Antagonist: Reduces the dose required for smoking

*Significantly higher quit rate vs. bupropion or placebo at 12 weeks. 2,14

Favourable safety and tolerability profile in approximately 4,000 treated smokers 2

Pfizer
sunbathing or a picnic. If untreated, the natural history of the disease is biphasic; the inflammatory lesions resolve in days to weeks, but the pigmentation may last months or even years.21

Bergapten, or 5-methoxypsoralen, is the photoactive component of bergamot oil from the bergamot lime (Citrus bergamia), which is a popular ingredient in perfumes and fragrances. Apart from its existence in cosmetics and other toiletries it may also be found in soap, household cleaners, detergents, air fresheners, and other related items. Besides the bergamot lime, bergapten is a naturally occurring component of various other fruits and plants. Examples of these are figs (Ficus carica), celery (Apium graveolens), lemon oil and Queen Anne’s lace (Ammi majus).22

Pseudoporphyria

Pseudoporphyria may occur with some medications, the most common of which is naproxen.23,24 Other medicines associated with pseudoporphyria are nalidixic acid, tetracycline, fusidic acid, bumetanide, amiodarone, cyclosporine, pyridoxine and dapsone.14 Frequent use of sun-tanning beds and chronic renal failure are other predisposing factors.

Pseudoporphyria is clinically characterized by increased skin fragility; erythema; and the appearance of tense bullae and erosions on sun-exposed skin, which are identical to those seen in patients with porphyria cutanea tarda. However, a clinical pearl that may prove helpful in differentiating between pseudoporphyria and porphyria cutanea tarda is that the classic features of hypertrichosis, hyperpigmentation, and sclerodermoid changes found with porphyria cutanea tarda are unusual with pseudoporphyria. The results of porphyrin studies are normal.21

The primary treatment of pseudoporphyria is to discontinue the offending agent whenever possible. Resolution of the clinical findings of drug-induced pseudoporphyria may take many months. Some patients may be left with permanent scarring.21

Lichenoid reactions

Lichenoid reactions that occur in a photodistribution are often difficult to distinguish from idiopathic lichen planus.25 These reactions are characterized by violaceous or erythematous papules and plaques that sometimes have Wickham striae [whitish lines visible in the papules of lichen papules and other dermatoses,] Hydrochlorothiazide, hydroxychloroquine, enalapril, demeclocycline and captopril are known causes of drug-induced lichenoid reactions.

Lupus-like reactions

Drug-induced photosensitivity reactions may also include lupus-like reactions. Such reactions may resemble subacute cutaneous lupus erythematosus because of their scaling, annular, and psoriasiform characteristics.

Hydrochlorothiazide is the drug most frequently associated with this reaction but calcium channel blockers, ACE inhibitors, griseofulvin, and terbinafine are other agents that have been implicated.23,24 The rate of reaction is low for any of these agents.

Photoaggravated tattoo reactions

Photo-aggravated tattoo reactions are most commonly caused by yellow (cadmium sulfide) tattoo pigment. Oedema and erythema may develop upon exposure to sunlight. Although the mechanism is not clear, cadmium sulfide is the light-sensitive material used in photoelectric cells; therefore, the reaction is believed to be phototoxic.

Red tattoos [red dye is mercuric sulfide (cinnabar), sienna (ferric hydrate), sandalwood, brazlwood, organic pigments (aromatic azo compounds)] have been associated with photo-aggravated tattoo reactions less frequently than yellow tattoos, and most likely, these reactions are related to the trace amounts of cadmium added to brighten the red pigment. In contrast to hypersensitivity reactions to red tattoos, reactions to pigments used to create green [chromic oxide, lead chromate, phthalocyanine dyes], blue [cobalt aluninate] and black [carbon (India ink), iron oxide, logwood] tattoos are much less common.21

Treatment and prognosis of photosensitivity reactions

The mainstays of treatment of drug-induced photosensitivity include identification and avoidance of the causative agent, the use of sun protection, and symptomatic relief.

Topical corticosteroids and cool compresses may alleviate drug-induced photosensitivity. In severe cases systemic corticosteroids may be utilized.

If sunscreens are not the cause of the photosensitivity, they should be used liberally. The sun protection factor (SPF) may not be a reliable indicator of protection against drug-induced photosensitivity. The SPF refers to the degree of protection against sunlight-induced sunburn, primarily that caused by UV-B. Most drug-induced photosensitivity reactions are caused by wavelengths within the UV-A range. Therefore, sunscreens that absorb UV-A should be prescribed. Sunscreens that contain avobenzene, titanium dioxide, and zinc oxide are more effective in blocking out UV-A radiation than sunscreens that contain other ingredients.8

In most patients, the prognosis is excellent once the offending agent is removed. However, complete resolution of the photosensitivity may take several weeks to months. Occasionally, patients may have persistent light reactivity for which the prospects for resolution may be poor.25

Patient Education

Patients need to be counseled regarding the possible photosensitizing properties of both prescription and nonprescription medications.

Most often, appropriate sun protection measures may prevent most drug-induced photosensitivity reactions. Some practical information on the use of sunscreens may be found in Table 3

Conclusion

All health care professionals should make an effort to educate their patients and clients and raise the awareness to photosensitivity reactions as well as necessary prevention measures. Healthcare professionals should also be aware on how best to use sunscreens in an effort to prevent as much as possible the occurrence of photosensitivity reactions
References:


Practice points

- Sunscreens should be applied 30 minutes before exposure for full skin exposure and should be applied thickly for maximum water-resistance

- One application is NOT enough. Experiments show a time-dependent decrease in Sun-Protection Factor [SPF] within the first few hours after sunscreen application. Swimming and perspiration also reduce the SPF value for many sunscreens

- Sun-screen should be applied after sweating, swimming, towel and hiking [clothing rubs it off exposed arms and legs]. Sunscreen should generally be reapplied every 40-80 minutes

- Re-applying sunscreen during the day does NOT extend the period of protection. SPF 30 means a maximum of SPF 30 protection under ideal conditions and frequent reapplications

- The SPF is the amount of UV radiation required to cause sunburn on skin with the sunscreen on, relative to the amount required without the sunscreen. So, wearing a sunscreen with SPF 30, one’s skin will not burn until it has been exposed to 30 times the amount of solar energy that would normally cause it to burn

- SPF applies to UVB rays only. It does NOT apply to UVA. An SPF 30 product with NO UVA screen will be less effective than a product with a lower SPF value which contains a UVA screen

- Sunscreens should be applied to all exposed areas of the skin, including overlooked areas such as back of the neck, tops of the feet [if in sandals] and the rims of the ears

- Multi-day exposure to sunlight increases UV sensitivity on subsequent days of exposure. Higher SPF products must be used in such cases

- DEET-containing insect repellents may decrease a product’s SPF by approximately 30%. Sunscreens can increase skin absorption of DEET

- Children receive 50-80% of their lifetime exposure to UV rays by the time they are 18 years old. Sunscreens should thus be used early


Sun and sea in summer

Victor Grech MD, PhD, FRCPCH, MRCP(UK), DCH, CLJ

Consultant Paediatrician (Cardiol), Department of Paediatrics, Mater Dei Hospital, Malta
Associate Professor of Paediatrics, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
Email: victor.e.grech@gov.mt

Educational aims

• To highlight prevention strategies and management of over exposure to the sun
• To provide an overview of eye and ear infections frequently encountered in the summer months
• To provide an insight into jellyfish stings and their management

Key words
otitis media, otitis externa, conjunctivitis, bacterial, sunstroke, sunburn

Summer is upon us soon, and we will encounter patients with various ailments which tend to be specific to this time of the year. OTC (over the counter) treatment may or may not be appropriate and this article will give some reasonable guidelines.

Introduction

Being outdoors in summer exposes individuals to a variety of environments that the body is normally unaccustomed to for most of the year. These are namely intense sunlight and swimming (sea water or pools). This article will highlight some common problems that may be encountered in these settings.

Solar exposure

The sun produces visible light and heat, but these comprise only a part of the solar radiation spectrum. The portion of the solar spectrum that leaks through the atmosphere and produces skin damage is the ultraviolet portion and this radiation produces both short term and long term damage.

Short term damage is comprised literally of skin burns. These may be of varying degrees depending on the strength and duration of exposure. These burns may therefore be of 1st or 2nd or even 3rd degree. 1st degree burns causes redness and pain within a few hours after the exposure, with worsening of the symptoms over the next twenty-four hours. 2nd degree burns are more severe and serious, and can also cause blistering of the skin (Figure 1).

Treatment of sunburns involves control of pain and includes the use of paracetamol or stronger pain relief, such as ibuprofen, for a few days. One may also use moisturizers and a 1 percent hydrocortisone cream three times a day, cool baths and wet compresses. Drinking lots of fluids is also important. If peeling occurs, one may continue to apply moisturizers until the skin heals.

With regard to long term effects, unfortunately, we receive most of the solar damage to our skin as children, and this damage is permanent and cumulative. Reducing this solar exposure decreases the chances of premature aging and also reduces the risk of skin cancer in the long term.

Prevention is always better than cure and some important reminders include:

• Ultraviolet radiation is also reflected from relatively bright surfaces such as sand and sea, so staying in the shade is not, by itself, sufficient.
• Protective clothing is crucial, including a hat and long sleeve shirt and long pants. Keep in mind that most clothing only has a protection factor of 5 to 9, so one can still get sun damage with clothing on.
• Limit exposure to the sun when it is at its strongest, between 10am and 4pm.
• It is also important to protect eyes with sunglasses.
• Sunblocks should be used daily, even under cloudy conditions, since most of the sun’s radiation penetrates clouds and can still cause sunburn.
• Sunblocks are the most important and effective anti-aging creams.
• A sunscreen should contain ingredients that physically block the sun’s radiation, especially for sensitive skin. Such compounds include zinc oxide and titanium dioxide.
• Deet is found in insect repellents and reduces the effectiveness of sunblocks, so use a higher factor of sunblock if using a combination product that has both a sunscreen and an insect repellent.
Sunstroke
Sunstroke or heatstroke are an advanced form of hyperthermia, a progression from heat exhaustion or heat prostration. Hyperthermia comes from the Greek hyper, meaning ‘over, above, or excessive’ and the Greek therme, meaning ‘heat’. It is an acute condition and a medical emergency wherein the body is overheated because it produces or absorbs more heat than it can get rid of. This condition is most commonly caused by prolonged exposure to excessively high temperatures and results in the body’s heat-dissipating becoming literally overwhelmed and unable to effectively lose heat, and the body’s core temperature spirals upward uncontrollably. Hyperthermia may also be caused deliberately in the treatment of certain forms of cancer, or inadvertently as a rare reaction to certain drugs during general anesthesia. Hyperthermia differs from fever that fever is a natural body reaction and is, to some extent, controlled by the body itself. Temperature is set (normal or fever) by the action of the pre-optic region of the anterior hypothalamus, deep within the brain, and this is usually a normal immune response to a bacterial or viral infection, allowing the immune system to work more effectively and to degrade and weaken the condition of the invading organisms. In contrast, hyperthermia occurs when the body temperature is raised without the consent of the heat control center. Hence, hyperthermia may be defined as a temperature rise above and beyond that required by and regulated.

Figure 1. Layers of skin affected by increasing severity of burns

Figure 2. Conjunctivitis with a red eye and purulent discharge

Figure 3. Otitis externa with inflammation and swelling of the lining of the external auditory canal and a discharge leading out of the ear

Figure 4. Normal ear on the right and otitis media on the left showing the middle ear cavity inundated with pus, causing the eardrum to bulge into the external auditory
by the body’s thermoregulatory mechanisms. One of the body’s most important temperature regulation systems is the process of sweating. The skin engorges with blood and the appearance is that of flushing. This process draws heat from inside as the skin acts as a radiator, allowing heat to be carried off by radiation or convection. Evaporation of sweat further cools the skin. However, when the body becomes dehydrated, the production of sweat ceases and in an attempt to maintain blood pressure, blood may be diverted from the skin back to the central vascular system, and at this point, when heat cannot be lost, the core temperature rises literally uncontrollably.

Affected individuals may become confused and hostile and appear intoxicated since brain function becomes impaired. They may also complain of headaches and may feel faint due to a drop in blood pressure. The heart rate and respiratory rate rise and as the victim also goes into shock, the appearance of a flushed skin changes to that of a pale, cold and clammy skin. Chills and trembling may also occur along with nausea and vomiting, and convulsions may ensue. As the internal organs begin to fail (kidneys, liver etc) unconsciousness and coma will result, followed by death.

If we were to quantify some temperature figures, the normal human body temperature is up to 37.5°C (99°F). Temperatures above 40°C (104 °F) are life-threatening and at 41°C (106 °F), brain death ensues. Death is almost certain at 45°C (113°F).

Heat stroke is a medical emergency requiring hospitalization. First aid requires the immediate lowering of the body temperature, by moving indoors or into the shade, the removal of clothing, and cooling the skin by wetting with cool water or by the application of cold and or wet compresses. Alcohol rubs should not be used. A fan will help to evaporate the water on the skin and further aid cooling. Rehydration is also crucial by drinking water or commercial isotonic solutions. Once admitted to hospital, these measures will be continued along with an infusion of intravenous fluids to correct dehydration. Needless to say, avoidance is crucial. In the setting of hot environments, one should drink lots of fluids, wear light, loose-fitting clothing and wide brimmed hats, avoid direct sunlight, use sunscreens and avoid unnecessary exertion in conditions of relatively high heat. Use fans and other methods of active cooling. Alcohol and caffeinated drinks should be avoided as these promote the production of excessive urine, worsening water loss.¹

**Otitis and conjunctivitis**

In summer, pools and contaminated seawater may predispose to eye or ear infections.²,³,⁴

Conjunctivitis is characterised by painful red eyes with a purulent discharge (Figure 2). These may sometimes be treatable with just saline washes and simple analgesia with paracetamol. However, these measures may not suffice and it is not unreasonable to administer antibiotic eye drops (three times daily for a week) along with saline cleaning. Persistent pain/redness/discharge should prompt medical referral. Never use a steroid containing eye preparation as if the infection is viral, severe damage may be incurred. Moreover, persistent usage of steroid eye drops may lead to serious complications, such as high intraocular pressure.

**Ear infections**

Ear infections may be of two types:

- **Otitis externa** is an infection of the external auditory canal, and leads to pain in the ear canal along with a discharge that mixes with ear wax and therefore appears brownish-yellow (fig 3). Again, in such cases, it would not be unreasonable to administer a topical antibiotic preparation along with simple analgesia such as with paracetamol. Naturally, persistent pain/discharge should prompt medical referral.

- **Otitis media** is more likely to occur in winter and causes a very painful infection of the ear middle ear cavity, often associated with an intercurrent cold. However, such infections may also occur when contaminated sea or pool water reaches the ear through the nose – through the communication called the Eustachian Tube that connects the middle ear cavity with the back of the mouth, and it is this communication that allows us to equalise the pressure within the ear when we fly, and also allows infections to reach the ear from the mouth in the setting of a cold or when diving into contaminated water (Figure 4). Analgesia should be prescribed for the severe pain until a medical review is available. These infections occur behind the ear drum and therefore cannot be reached by ear drops as these are stopped by the ear drum, which is both air- and water-tight.

Untreated otitis media may cause the build-up of pressure by pus within the ear to actually rupture the ear drum, liberating pus into the ear canal where it mixes with ear wax and appears as a brownish-yellow discharge. This relieves the pressure and therefore the pain, and in this setting, ear drops will actually reach the middle ear cavity through the perforation. Such perforations are usually self-sealing.

**Jellyfish**

Jellyfish blooms seem to be becoming an annual event, not only in Malta, but throughout the Mediterranean, and therefore, as in previous years, it is likely that the Maltese islands will see their customary share of jellyfish this summer, particularly on days when sea currents and winds waft large offshore blooms toward our shores.

There are several theories why the local jellyfish, the Pelagia noctiluca is becoming a frequent visitor to our coasts. The main reason is probably that fishing is removing the jellyfishes’ main competitor for food, thus leaving more food for the jellyfish to feed on. Moreover, global warming, by heating up the seas, speeds up the production of the microscopic organisms on which jellyfish feed. Overfishing also leads to a decrease in natural jellyfish predators, such as marine turtles, which are also often victims of vessel propellers.

Jellyfish are stinging aquatic invertebrates. Most jellyfish are harmless to humans but a few can cause serious problems. Jellyfish have stinging organelles (nematocysts) which may penetrate the upper dermis and discharge venom which causes a local reaction and may also diffuse into the systemic circulation. The venoms are typically polypeptides and enzyme compounds which may be both toxic and antigenic to humans.⁵ The most common adverse reactions are mild local dermatitis. Rarely serious or fatal systemic reactions may occur.

The Pelagia noctiluca is an oceanic species widely dispersed in warm waters, and can grow up to 10 centimetres in diameter with mauve or pink mushroom-shaped body. The tentacles total eight in all, and are pale with mauve or pink mushroom-shaped body. Jellyfish have stinging organelles (nematocysts) which may penetrate the upper dermis and discharge venom which causes a local reaction and may also diffuse into the systemic circulation. The venoms are typically polypeptides and enzyme compounds which may be both toxic and antigenic to humans.⁵ The most common adverse reactions are mild local dermatitis. Rarely serious or fatal systemic reactions may occur.

The Pelagia noctiluca is an oceanic species widely dispersed in warm waters, and can grow up to 10 centimetres in diameter with mauve or pink mushroom-shaped body. The tentacles total eight in all, and are pale brown and usually between 10cm and 30cm in length. When the jellyfish comes into contact with its prey, or with a potential predator, it fires its stings from poison sacks and the stinging cells latch onto the skin to leave a burn. The sting is painful and
can be dangerous to the few individuals who are particularly sensitive to them. In this species, even the body stings. Caution jellyfish should be discarded in refuse bins as detached tentacles left on the beach remain capable of stinging for several weeks.

The effects of Pelagia noctiluca stings are usually limited to the skin causing erythematous, edematous, and vesicular topical lesions with local pain which persists for 1–2 weeks, and systemic complications or cutaneous superinfections.

Rarely, dramatic immediate reactions have been observed after Pelagia noctiluca stings and these include severe generalized allergy with bronchospasm, pruritus and postinflammatory hyperpigmentation. Immediate pain, distress and the occurrence of urticarial lesions and dyspnoea after massive stings have been reported. Stings may also leave scars and hyperpigmentation that may last for years.11

### Practice points

- Avoid the sun whenever and wherever possible.
- Drink lots of water and use protective clothing and sunblock.
- Alcohol and caffeinated drink exacerbate dehydration.
- Skin damage from solar exposure is cumulative.
- Only doctors should (cautiously) prescribe steroid containing eye drops.

There are no deterrents to jellyfish stings. Tentacles and wounds should also be rinsed with saline/sea water and not fresh water. Adherent tentacles should be gently lifted off with a towel or stick in order to prevent progressive envenomation. Heat worsens the burn so they should not be rubbed with sand. The most effective first aid treatment for the skin pain of jellyfish wounds is the use of cold packs. Cold packs should be applied to the stung area for fifteen minutes and then re-applied, if necessary.

In summary, while summer is fun, the potential for risky behaviour and for accidents and injury is higher, as individuals have more time for recreation and for leisure activities that they would other not be able to perform. Care should be taken in order to avoid not only short term problems, such as jellyfish bites and painful sunburn, but also long term complications due, for example, to solar exposure, such as skin cancers.

### References

a turning point for weight loss

real evidence – alli is orlistat 60 mg, the first and only EU-licensed non-prescription weight loss treatment.

real help – alli combines a capsule and a support programme to help users lose 50% more weight than by diet alone.

real benefits – alli brings positive change to customers and the opportunity for you to recommend with confidence.

Product Information.

alli 60 mg hard capsules (orlistat).

Indication: Weight loss in adults BMI ≥ 28.

Dosage: Adults (18 or over): One capsule with each of three main meals. Max. 3 capsules for up to 6 months. Use with mildly hypocaloric, lower-fat diet. If no weight loss within 12 weeks, refer to doctor or pharmacist. Diet and exercise should start prior to treatment. Contraindications: Hypersensitivity to ingredients; concurrent treatment with oral anticoagulants or ciclosporin; chronic malabsorption syndrome; cholestasis; pregnancy; breast-feeding.

Special warnings and precautions: Talk to doctor before starting to take alli if taking amiodarone, a medicine for diabetes, epilepsy or hypothyroidism, or if patient has kidney disease. If taking a medicine for hypertension or hypercholesterolaemia, talk to doctor or pharmacist when taking alli. Risk of gastrointestinal (GI) symptoms increases with fat consumption. Take multivitamin at bedtime. See doctor if rectal bleeding occurs. Oral contraceptive efficacy may be reduced if severe diarrhoea occurs; use additional contraception.

Drug interactions: Ciclosporin; oral anticoagulants; levothyroxine; antiepileptic medication; oral contraception; fat soluble vitamins; acarbose; amiodarone. Pregnancy and lactation: Do not use during pregnancy or lactation. Side effects: See SPC for full details. Predominantly GI e.g. oily stools, urgency; usually mild and transient, risk reduced by low fat consumption. Diverticulitis; pancreatitis; mild rectal bleeding; hepatitis; cholecystitis; abnormal liver enzymes; anxiety; hypersensitivity reactions including anaphylaxis, bronchospasm, angioedema, pruritus, rash; and urticaria, bullous eruption. Legal category: Non-prescription.

Find out more at www.alli.com.mt

alli is a registered trademark of the GlaxoSmithKline group of companies.
Causes of cough

Lorna Marie West BPharm(Hons), MSc Clin Pharm(Aberdeen)

Senior Clinical Pharmacist, Mater Dei Hospital, Tal-Qroqq, Malta
Chairperson of Publications, Malta College of Pharmacy Practice
Email: lorna.m.west@gov.mt

Educational aims
• To have a better understanding of the various causes of cough
• To provide an overview of the different types of cough
• To enable better assessment of a patient presenting with cough

Key words
cough, acute, chronic, productive, dry

A cough, being acute or chronic, is a symptom of a variety of respiratory and non-respiratory conditions and pharmacists should be able to distinguish between a cough not resulting from a serious pathology and one which could be the underlying symptom of a potentially critical condition.

Introduction
Patients frequently present to pharmacists requesting medications which can relieve cough, describing it mainly as productive or dry. A cough is a symptom of a variety of respiratory and non-respiratory conditions which could be both mild and serious in nature and can be described as "a forced expulsive manoeuvre or manoeuvres against a closed glottis that are associated with a characteristic sound or sounds".

Causes of cough can range from a common cold to malignancy and pharmacists should be able to distinguish between a cough not resulting from a serious pathology and one which could be the underlying symptom of a potentially critical condition. Studies have shown that the reporting of cough is more prevalent in females than males, possibly due to an increased sensitivity of cough reflex in women.

Types of cough
An acute cough is often the result of an upper respiratory tract infection and although distressing it is usually self-limiting and does not require any medical intervention. An acute cough is defined as one lasting less than three weeks. When a patient presents with an acute cough the pharmacist should still enquire about haemoptysis, the possibility of an inhaled foreign body and prominent systemic illness since cough can be the first indication of an underlying serious condition. Table 1 refers to some of those instances when the pharmacist should refer the patient to a doctor. Common causes of an acute cough are upper respiratory tract infections, exacerbations of chronic obstructive pulmonary disease (COPD), allergic rhinitis, and rhinitis due to environmental irritants and asthma which is not well controlled.

A chronic cough is one which lasts more than 8 weeks and accounts for one-tenth of respiratory referrals to secondary care. Cough lasting between three to eight weeks is defined as subacute cough. In general, most chronic coughs are dry or minimally productive in nature although some pathologies result in a chronic cough with the presence of significant sputum production. Although chronic cough is perceived as trivial, it can be a disabling symptom associated with significant morbidity. Pharmacists should perform a detailed history in all patients presenting with a chronic cough as explained in Table 2 and should refer such patients to a specialist. Chronic cough would have started off as an acute cough and therefore it is important to identify the exact duration of this symptom so as to narrow the list of possible causes. Some of the most common causes of chronic cough in immunocompetent patients are asthma, gastro oesophageal reflux disease, chronic bronchitis due to cigarette smoking and other irritants, bronchiectasis, eosinophilic bronchitis, postnasal-drip syndrome from conditions of the nose and sinuses, or the use of an angiotensin-converting-enzyme (ACE) inhibitor.

Some physical symptoms can occur as a consequence of cough, such as musculoskeletal pains, hoarseness, stress incontinence, blackouts and vomiting. Therefore, patients presenting with an unknown cause of the afore-mentioned physical symptoms should be asked about a history of coughing.
Medical, Laboratory
Equipment & Supplies

· Sourcing and Supply of all types of Medical and Laboratory equipment.

· Turnkey contracting for Hospitals, Industrial and Clinical laboratories.

· Analytical Equipment for R&D facilities and Quality Control departments.

· Testing and Calibration facility for Industry.

· Tailor made solutions with guaranteed Quality Maintenance service.

· Medical Products for Home use for better quality of life especially for senior citizens and disabled persons.

· Trained staff always at hand to help and advise you.

Technoline
Serving Medicine and Science since 1978

51, Edgar Bernard Street, Gżira GZR 1703 - Malta
Tel: 21 344 345    Fax: 21 343 952    admin@technoline-mt.com
Showroom: 68, Nazju Ellul Street, Gżira
Opening Hours: 8.00am to 5.00pm - Monday to Friday
www.technoline-mt.com
potentially result in psychological distress such as depression and can have an impact on the patient’s social well being such as avoidance of public places.¹

**Common causes of cough**

When patients present with a troublesome cough, their main goal is to eliminate the symptom as quickly as possible.¹ Patients may have more than one factor contributing simultaneously to cough. Treatment for the different aetiologies described below may not always be as simple as dispensing a cough preparation. Treatment of different conditions may vary from the prescribing of antihistamines and nasal decongestants to the use of inhaled or oral corticosteroids or at times antibiotics. At other times patients presenting with cough will require complex treatment depending on the underlying condition. Moreover, the FDA strongly recommends that infants and children under 2 years of age should not be given over the counter cough preparations.² The aim of this paper is to emphasise that there are multiple contributing factors to cough and that it should not always be treated empirically with cough preparations.

The following are just a few of the most common causes of cough:

- **Angiotensin-Converting-Enzyme (ACE) Inhibitor induced cough**

  One of the most common causes of a dry, non-productive persistent cough, which could be easily detected by a pharmacist, is the one caused by angiotensin-converting-enzyme (ACE) inhibitors. ACE inhibitors can cause bradykinin accumulation within the upper airway and decreased metabolism of proinflammatory mediators, and can therefore act as irritant substances in the airways to increase bronchial reactivity and induce cough. ACE inhibitor-induced cough can present a few hours and up to months after initiation of treatment. Cessation of ACE inhibitor therapy will result in cough resolution. However, cough can take up to few months to resolve.² Since cough due to ACE inhibitors is a class-effect and not dose-related, substituting one ACE inhibitor for another might not improve the cough. Therefore, the ACE inhibitor should be substituted by an angiotensin II receptor antagonist in an attempt to resolve the cough.³

### Table 1. Symptoms associated with acute cough which require prompt referral

<table>
<thead>
<tr>
<th>Patients presenting to a pharmacy with an acute cough should be referred when one of the following is also present:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fever</td>
</tr>
<tr>
<td>• Haemoptysis</td>
</tr>
<tr>
<td>• Shortness of breath</td>
</tr>
<tr>
<td>• Chest pain</td>
</tr>
<tr>
<td>• Weight loss</td>
</tr>
</tbody>
</table>

### Table 2. In a patient presenting with a chronic cough the pharmacist should determine:

| • Age and gender |
| • Smoking status |
| • Onset of cough |
| • Duration of cough |
| • Cough in relation to infection |
| • Presence of sputum |
| • Diurnal variation in cough |
| • Severe coughing spasms/paroxysms |
| • Incontinence |

- **Asthma, COPD, Acute bronchitis, Chronic bronchitis and Eosinophilic bronchitis**

  Acute cough is one of the most common symptoms associated with loss of asthma control, acute exacerbations of asthma and COPD. In cough variant asthma, cough may be the only presenting manifestation⁴ and the treatment is the same as asthma in general.⁵ The most common cause of COPD is cigarette smoking. Common signs and symptoms of COPD are shortness of breath, cough and/or mucus production.⁶ Routine treatment with antibiotics in these patients is not justified. Acute bronchitis is an acute respiratory infection with a normal chest radiograph that is manifested by cough with or without phlegm production that lasts up to three weeks.⁷ Most patients with acute bronchitis should not be given β₂-agonist bronchodilators to alleviate cough. In acute bronchitis patients may insist on receiving an antibiotic. The decision of whether to use antibiotic or not should be addressed individually and explanations should be given to the patient.⁸ Chronic bronchitis is a condition that is manifested by cough and sputum expectoration occurring on most days for at least 3 months of the year and for at least 2 consecutive years when other respiratory or cardiac causes for the chronic productive cough are excluded.⁹ Non-asthmatic eosinophilic bronchitis is characterised by the presence of eosinophilic airway inflammation similar to that seen in asthma.¹⁰ It is a cause of chronic cough which is distinct from asthma since it is not associated with bronchial hyperresponsiveness or variable airflow obstruction.¹¹ Cough associated with eosinophilic bronchitis can be dry as well as productive in nature. Respiratory irritants, such as personal tobacco use and passive smoke exposure, should be avoided.

- **Environment and smoking induced cough**

  Exposure to pollutants and environmental irritants can be a cause of chronic cough.¹² One of the commonest causes of a persistent cough is smoking. One study observed nocturnal cough in relation to indoor exposure to cat allergens.¹³ Therefore, patients presenting with cough should be asked about occupational and environmental causes.

- **Gastro-oesophageal reflux disease (GORD)**

  Gastro-oesophageal reflux disease, alone or in combination with other conditions, is one of the most common causes of
chronic cough. A cough in the absence of gastrointestinal symptoms may be the only presenting complaint in patients suffering from GORD, since there may be no gastrointestinal symptoms up to 75% of the time. It may take two to three months of intensive medical therapy before cough starts to improve and on average five to six months before the cough resolves. Therefore, it is incorrect to assume that cough is not caused by GORD when gastrointestinal symptoms improve or disappear but the cough remains unchanged. When treating GORD other co-morbidities have to be kept in mind such as obstructive sleep apnoea or coronary artery disease.

**Heart failure**
Acute cough can be the presenting sign of heart failure in patients who have pulmonary congestion. Therefore, since cough can be a symptom of pulmonary oedema it is important to have a high index of suspicion of left ventricular heart failure in elderly patients presenting with a new or worsening cough, and refer such patients to a specialist.

**Malignancy**
Patients presenting with cough and have risk factors for lung cancer should be referred to a specialist. Cough may be due to the cancer itself, the treatment, or other co-existing disease. Malignancies which arise in other organs will often metastasize to the lungs and therefore patients with a history of a malignancy should be referred for specialist advice.

**Upper respiratory tract infections**
Upper respiratory tract viral infections are one of the most common causes of acute cough, which appears to arise from the stimulation of the cough reflex in the upper respiratory tract by postnasal drip, clearing of the throat, or both. Post-infectious cough starts with an acute respiratory tract infection that is not complicated by pneumonia and ultimately resolves without treatment. A post-infectious cough is present for at least 3 weeks following an acute respiratory infection, but not more than 8 weeks. There are multiple pathogenic factors which may contribute to the cause of cough and therefore therapy depends on the cough provoking factor.

### Practice points
- An acute cough is one lasting less than three weeks whilst a chronic cough is one which lasts more than 8 weeks.
- The pharmacist should enquire about haemoptysis, the possibility of an inhaled foreign body and prominent systemic illness in a patient with an acute cough.
- Pharmacists should perform a detailed history in all patients presenting with a chronic cough and should refer such patients to a specialist.
- There are multiple contributing factors to cough and pharmacists should not always treat empirically with cough preparations.
- Infants and children under 2 years of age should not be given over the counter cough preparations.

### Conclusion
Coughing is a distressing symptom and chronic cough is an important medical and economic problem. In patients complaining of cough the pharmacist should evaluate for a variety of complications associated with coughing prior to dispensing cough preparations. Moreover, the pharmacist should refer patients for specialist advice when there is the possibility of an underlying condition.

### References
Celebrating 15 years of Customer Loyalty

Valletta Fund Management Limited ("VFM") would like to thank its clients for their loyal support over the past 15 years, enabling the Company to position itself as the leading fund management company in Malta.

Set up in 1995, VFM, which is jointly owned by Bank of Valletta p.l.c. and Insight Investment Management (Global) Limited, currently holds €787 million* in assets under management represented by over 34,000* shareholders.

VFM is committed to focus on customer needs and to continue to provide innovative investment solutions for investors.
Pain management in palliative care - choice of analgesia

Helen McClay  BPharm(Hons), Dip Pharm Prac, MSc (Oncology), DMS, MRPharmS
Principal Pharmacist, Basildon and Thurrock University Hospital NHS FT, UK.
E-mail: helen.mcclay@btuh.nhs.uk

Pain can be classified broadly into two categories, nociceptive and neuropathic, characterised by different clinical presentations and underlying pathophysiological mechanisms. (Table 1)

The WHO analgesic “ladder”

The WHO guidelines were first published in 1986 and are considered to be the gold standard for managing pain in advanced cancer. Figure 1 gives a schematic diagram of the recommended “analgesic ladder”

Non-opioids include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and adjuvant analgesia. Adjuvant drugs include antidepressants, anticonvulsants, antispasmodics, steroids and bisphosphonates.

Educational aims

• To provide an overview of common analgesia used in the management of cancer pain
• To provide a basic understanding of the pharmacology of these drugs and their place in therapy

Keywords
pain, opioids, analgesia, cancer

Educational aims

• To provide an overview of common analgesia used in the management of cancer pain
• To provide a basic understanding of the pharmacology of these drugs and their place in therapy

Pain can be classified broadly into two categories, nociceptive and neuropathic, characterised by different clinical presentations and underlying pathophysiological mechanisms. (Table 1)

The WHO analgesic “ladder”

The WHO guidelines were first published in 1986 and are considered to be the gold standard for managing pain in advanced cancer. Figure 1 gives a schematic diagram of the recommended “analgesic ladder”

Non-opioids include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and adjuvant analgesia. Adjuvant drugs include antidepressants, anticonvulsants, antispasmodics, steroids and bisphosphonates.

Choice of analgesia
Non-opioid

• Paracetamol

Despite being a widely used drug and available for a very long time, the mechanism of action for paracetamol still remains unclear. The standard explanation is that it acts as a cyclo-oxygenase inhibitor in the brain, explaining both its analgesic and its antipyretic properties. It is also thought to be involved with serotonin modulation pathways. Ultimately paracetamol remains a safe, well tolerated and effective drug especially in the management of mild to moderate pain. It can also be administered with other analgesia to achieve an additive effect. The main problem is hepatotoxicity especially in overdose.

• Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are useful in treating mild to moderate pain mediated by prostaglandins, which serve to sensitise nociceptors. They are of particular benefit for pains associated with inflammation. In spite of insufficient evidence, NSAIDs have traditionally been used in the palliation of metastatic bone pain although radiotherapy remains the treatment of choice.

NSAIDs inhibit cyclo-oxygenase (COX), an important enzyme in the arachidonic acid cascade which results in the production of tissue and inflammatory prostaglandins. COX exists in two forms. COX-1 is constitutive i.e. is part of the body’s normal physiological constitution with near constant levels and activity in most tissues, including the central nervous system (CNS). COX-2 expression is generally low or non-existent but is inducible i.e. is massively produced within a few hours by inflammation. The main exceptions to this are parts of the central nervous system (CNS), kidneys and seminal vesicles which contain high levels of COX-2 (Figure 2).

Non-specific COX inhibitors, such as aspirin, ibuprofen, diclofenac and naproxen inhibit both isoenzymes to produce analgesia. However this also leads to adverse effects typically observed as gastrointestinal and renal toxicity.

Opioids

Opioids include all drugs that act at opioids receptors, (mu, kappa, delta and ORL-1), distributed in varying densities throughout the body, particularly in the nervous system. Agonism at these receptors produces analgesic effects observed with opiates.

Codeine is usually the drug of choice for mild to moderate pain (step 2, WHO analgesic ladder). Its analgesic effect is largely due to its metabolism to morphine by cytochrome CYP2D6. Codeine is considered one tenth as potent as morphine. As a general rule, products containing less than 30mg of codeine per dose are not suitable step 2 analgesia. Although classified as a weak opioid, patients taking codeine stil present with typical opioid adverse effects including nausea, vomiting, sedation and constipation. However, unlike morphine weak opioids have a “ceiling dose”,
Table 1. Mechanism of pain and implications for treatment

<table>
<thead>
<tr>
<th>Type of pain</th>
<th>Mechanism</th>
<th>Examples</th>
<th>Typical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>Stimulation of nerve endings</td>
<td>Cramp, Soft tissue, bone pain, Liver capsule pain</td>
<td>Muscle relaxants, NSAIDs ± opioid</td>
</tr>
<tr>
<td>Somatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve compression</td>
<td>Pain transmitted from damaged neural tissue in either the peripheral or central nervous system</td>
<td>Neurora or nerve infiltration eg brachial or lumbosacral plexus, Spinal cord compression</td>
<td>Opioid + corticosteroid, Opioid, NSAID, tricyclic antidepressant, anti-epileptic, NMDA-receptor-channel blocker, spinal analgesia</td>
</tr>
<tr>
<td>Nerve injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De-afferentation pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central pain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Twycross R. Introducing Palliative Care, 4th Edition, Radcliffe Medical press 2003

Table 2. Commonly prescribed adjuvant analgesia in the management of cancer pain.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain</td>
<td>Amitriptyline, gabapentin, clonazepam, dexamethasone</td>
</tr>
<tr>
<td>Neuropathic pain (unresponsive to the above)</td>
<td>Ketamine</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>Hyoscine butylbromide, octreotide</td>
</tr>
<tr>
<td>Metastatic bone pain</td>
<td>Pamidronate, zolendronate, dexamethasone</td>
</tr>
</tbody>
</table>

Adapted from Twycross R et al. Palliative Care Formulary, Third edition, 2007

Figure 1. WHO 3-step Analgesia ladder

Figure 2. Products of arachidonic acid metabolism involved in inflammation

Key: COX – cyclo-oxygenase, 5-HPETE – hydroperoxyeicosatetraenoic acid, LOX – lipooxygenase, PG - prostaglandin
Non-specific COX inhibitors, such as aspirin, ibuprofen, diclofenac and naproxen inhibit both isoenzymes to produce analgesia. However this also leads to adverse effects typically observed as gastrointestinal and renal toxicity.

The starting dose of morphine depends on whether or not the patient has been previously exposed to opioids and at which dose. For opioid-naive patients, an immediate release formulation should be prescribed and the dose of morphine titrated according to response. Typically, 5 to 10mg every four hours is used with the option for further doses if the pain is not controlled with four hourly dosing. Once the morphine requirement over 24 hours is established, slow release preparation may be prescribed. The patient should be advised to expect sedation, nausea and vomiting during the titration period although tolerance develops with these adverse effects. However, tolerance does not develop to constipation and regular laxatives should be prescribed.

Strong opioid + non-opioid ± adjuvants

Weak opioid + non-opioid ± adjuvants

Non-opioid ± adjuvants
PROMOTING HEALTHCARE

A.M. Mangion Ltd (est. 1978) specialises in the importation and distribution of Internationally renowned Pharmaceutical and Healthcare products. Our corporate leadership and dedicated family of exceptional employees adhere to essential core values – chief amongst these are integrity, innovation, excellence, respect, accountability and teamwork.

A.M. Mangion Ltd provides the medical profession with an array of pharmaceuticals, medical devices, diagnostics and related products designed to holistically achieve wellness, prevention, treatment and cure in all sections of the healthcare industry.

Our O.T.C. (over-the-counter) products enhance the overall health and well-being and enable in-home treatment.

The main O.T.C. product categories are infant formulas, skin care, nutraceuticals, sun care and make-up.

The company’s commitment to providing medicine-safety education and an outstanding customer service to healthcare professionals and patients has been instrumental to A.M. Mangion Ltd’s success.

A.M. Mangion Ltd, Mangion Building, New Street off Valletta Road, Luqa LQA6000, Tel: 2397 6000 www.ammangion.com.mt
It has long been observed anecdotally that patients who develop intolerable adverse effects to morphine while achieving inadequate analgesia may sometimes benefit from switching to an alternative opioid. The initial dose of the second opioid depends on the relative potency of the two drugs. This again is a huge area of controversy and any equianalgesic tables should be considered with caution as there is lack of comprehensive data and inter-patient variation. Special caution should be exercised when converting a patient from high dose morphine to another opioid as the recommended equivalent doses become progressively less accurate as the dose increases. Therefore, when converting at high dose, it is best to give lower than the calculated equivalent doses and rely on “as required” doses to make up any deficit while re-titrating to a satisfactory dose of the new opioid. Some examples of alternative opioids are discussed below.

Oxycodone is a stronger opioid than morphine. Oxycodone is one and a half to two times more potent than morphine. Its opioid receptor site affinities remain controversial but apart from μ receptor activity it is thought to have agonist effects on receptors as well. Oxycodone is better tolerated than morphine especially in patients experiencing hallucinations. Similarly fentanyl is a stronger opioid than morphine. It has a low molecular weight and is lipophilic making it suitable for transdermal and oral transmucosal administration. Fentanyl patches are applied to the skin for 72 hours and a reservoir of fentanyl is formed in the fatty tissue under the skin. Analgesia is not achieved for at least 12 hours after the first patch is applied and steady state may not be achieved for up to 48 hours so analgesic benefit should not be assessed until three days after the first patch is applied. Once steady state is attained, the plasma half life can be up to 25 hours. Transdermal fentanyl can be considered an option for patients with renal impairment, severe constipation, dysphagia or bowel obstruction.

Methadone is reserved for patients with pain refractory to conventional treatment due to its complicated pharmacokinetics which can lead to accumulation. There is a lack of potency ratio between methadone and morphine and it should only be initiated by specialists in pain management. One major advantage is that methadone is also an N-methyl-D-aspartate (NMDA)-receptor channel blocker in addition to opioid agonism and has benefits in managing neuropathic pain.

Adjuvant analgesia

Adjuvant analgesia tend to be drugs that are licensed for indications other than pain. Hence they are not primarily classified as analgesia even though they may relieve pain that is usually not responsive to standard analgesia. These include steroids, anti-depressants, anti-epileptics, bisphosphonates and antispasmodics. Commonly prescribed adjuvant analgesia are listed in Table 2.

The choice of drugs depends on type of pain (nociceptive or neuropathic), co-existing morbidity and current medication. Adjuvants can also have opioid sparing effects and the opioid dose should be reviewed when initiating adjuvant analgesia. There is a risk of additive toxicity from polypharmacy, as adjuvant analgesia are typically administered to patients who are receiving several other drugs. The potential for additive side-effects must be considered prior to prescribing. The decision to add or continue a treatment must be based on a careful assessment of outcomes and a clear understanding of the goals of care.

Conclusion

Pain is one of the commonest symptoms of advanced cancer and probably the most dreaded by patients. However, the majority of patients with cancer pain can be well managed as long as analgesia is used appropriately and assessed regularly. Many patients are frightened of opioids, particularly morphine due to its possible connotations with death. It is vital to explore their fears before starting the drug and ensure that support is provided. Strategies should be in place to manage side effects as most can be easily managed but can have devastating effects if ignored or not addressed appropriately.

Practice points

- Pain is still one of the commonest symptom experienced by cancer patients, however it can be managed well in the majority of patients if the correct analgesia and appropriate dose escalations are used.
- The WHO analgesic ladder remains the gold standard for managing pain.
- NSAIDs have traditionally been used in metastatic bone pain, although evidence in this setting is limited. Radiotherapy remains the treatment of choice and these patients should be referred to oncology/palliative services to ensure best management.
- Patients should be counselled on adverse effects of opioids and appropriate medication prescribed to avoid preventable adverse effects.

References

Aspects of HIV infection and treatment

Daniela Mallia BPharm (Hons)
Clinical Pharmacist, Tal-Qroqq, Mater Dei Hospital
Email: daniela.mallia@gov.mt

Educational aims
- To familiarize pharmacists with the management of HIV
- To provide an overview of anti-retroviral therapy
- To highlight issues related to adherence and interactions

Key words
HIV, highly active anti-retroviral therapy (HAART), viral load, CD4 count, adherence.

Anti-retroviral therapy in the treatment of HIV (human immunodeficiency virus) aims to lower the viral load and improve immune function. Numerous interventions in the management of HIV seropositive patients are aimed to maximise individual patient adherence to treatment.

Introduction
The HIV pandemic has far exceeded projections over the past decade. At the end of 2008 there were:
- an estimated 33.4 million people living with HIV worldwide,
- an estimated 2.7 million new HIV infections, and
- an estimated 2.0 million AIDS (acquired immunodeficiency syndrome)-related deaths.¹

With regards to the local scenario, there were 30 new HIV infections and one AIDS-related death in Malta, in 2008.² In Malta, HIV testing is totally confidential, and is available free of charge to anyone.³ All patients are given a unique code number and only this number appears on all request forms. This procedure is used to eliminate the true identity of patients throughout the process – thus protecting confidentiality.

Aetiology and pathology of HIV
HIV is a retrovirus that infects cells of the immune system, leading to a specific decline in the CD4⁺ helper T cells. Immune responses to certain antigens begin to decline, and the host fails to adequately respond to opportunistic infections and normally harmless commensal organisms.

The widespread use of anti-retroviral therapy has had the most profound influence on reducing opportunistic infection-related mortality in HIV-infected persons. However, opportunistic infections remain a leading cause of morbidity and mortality in HIV-infected persons.

Anti-retroviral therapy
The goal of anti-retroviral therapy in HIV infection is to increase the length and quality of life by improving immune function. This is achieved by reducing the amount of replicating virus to as low a level as possible, for a long as possible, in all sites where HIV-infected cells are present, thereby preventing infection of new cells and further damage to the immune system. The amount of replicating virus in the plasma can be assayed by measuring the concentration of HIV RNA, referred to as the viral load. In practical terms, the aim of anti-retroviral therapy is to lower the viral load to a value below the level of detection of the assay used. Achieving this with the currently available anti-retroviral agents involves appropriate selection of combination regimens to obtain an antiviral response, and excellent adherence to the regimen by the patient. In addition, consideration of a plan for salvage or second line regimen is required if initial therapy fails.

There are eleven anti-retroviral agents currently being used in Malta (Table 1). These can be divided into three classes:
1. Nucleoside reverse transcriptase inhibitors (NRTIs)
   These were the first drugs to be licensed for the treatment of HIV infection. They are generally considered to be the backbone of anti-retroviral therapy when combined with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).
2. Protease inhibitors (PIs)
   A dramatic decline in the clinical progression of HIV disease and HIV-related deaths followed the introduction of PIs. The main drawbacks to PIs are the number of dose units that patients have to take, and the need for food restrictions.
3. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   These are the third class of drugs currently available to treat HIV infection. They are generally considered simpler to take than PIs, but are hampered by the fact that resistance develops quickly, and patients are usually resistance to all drugs within the class. These drugs act at different stages in the...
HIV replication cycle. The first anti-retroviral agent to become commercially available was zidovudine in 1987, followed by didanosine and zalcitabine in 1993 – all of which are NRTIs. Initially, these drugs were used alone as mono-therapy (often sequentially, as each agent became available). It is now realized that rapid resistance develops to anti-retroviral drugs if they are not used in combination. Effective combination therapy consisting of three or more anti-retroviral drugs, or highly active anti-retroviral therapy (HAART), is now the accepted standard of care for HIV-infected individuals requiring treatment.

Initiation of treatment

The CD4+ T-cell count (or CD4 count) serves as the major clinical indicator of immune function in patients who have HIV infection. It is one of the key factors in deciding whether to initiate antiretroviral therapy and chemoprophylaxis for opportunistic infections, and is the strongest predictor of subsequent disease progression and survival.

Most major guidelines (British, European and American guidelines) agree that antiretroviral therapy should be initiated in all patients with a CD4 count <350 cells/mm³. 4, 5, 6

Importance of strict adherence to treatment

HIV treatment is a chronic treatment and an expensive one too. Furthermore, strict adherence to an already complicated regimen is vital. Numerous international studies have concluded that less than 95% adherence is equivalent to treatment failure. Since most anti-retroviral drugs currently available exhibit cross resistance, development of resistance to a drug often means resistance to the entire class of drugs, thus limiting future treatment options.

It is fair to say that HIV infection is no longer considered the terminal illness that it was 5 to 10 years ago, but it is now regarded as more of a chronic infection, manageable with antiviral therapy. However, current knowledge indicates that the therapy should be for life, a situation that makes the issue of adherence a real obstacle for some patients.

A thorough understanding of HIV therapy, including the importance of good adherence and the dangers of poor adherence, is an important basic tool to increasing adherence. The importance of adherence is always stressed to all patients, including all new patients prior to initiating therapy.

Learning the patient’s daily routine and incorporating dosing cues into that routine is a very helpful tool to increase adherence. Patients are actively encouraged to discuss any problems with fitting their daily doses with their daily activities.

Partial adherence is extremely common. When assessing adherence of patients already on treatment, a neutral approach to adherence history is preferred. Questions like: “How many doses have you missed or taken more than an hour late, in the past month?” are preferred to “Have you taken all medications as instructed?”

New patients are informed that this new medication schedule might seem a bit complex initially, but they would eventually learn to fit it into their daily routine — and it will feel less complex.

Two typical regimens that are currently being used in the treatment of HIV involve:

- Lopinavir/ritonavir 200/50mg tablets, two tablets 12 hourly
- Zidovudine/lamivudine 300/150mg tablets, one tablet 12 hourly
- Efavirenz 600mg tablets, one tablet nocte
- Tenofovir 245mg tablets, one tablet daily
- Lamivudine 150mg tablets, one tablet 12 hourly

Effects and side effects of medication

Anti-retrovirals are not a cure for HIV – however, they can help reduce the chances of getting opportunistic infections associated with HIV. This fact is clearly explained to all patients – it is considered to be of utmost importance that all patients are aware that HAART does not kill the virus, but suppresses it to a minimal level.

As a consequence, patients are made aware that they can still transmit the virus to others. All HIV-infected patients (even those with viral loads below detection limits) are counseled to avoid sexual and drug-use behaviors that may lead to transmission or acquisition of HIV or other pathogens.

The pharmacist goes over the important beneficial effects and side effects of every

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effect</th>
<th>Management of side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Anaemia</td>
<td>Change to another NRTI with less incidence of this adverse event (e.g.) tenofovir</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crystalluria</td>
<td>Change to another PI with less incidence of this adverse event (e.g.) lopinavir/ritonavir</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rash</td>
<td>Change to another agent from the same class or a different class (e.g.) nevirapine or lopinavir/ritonavir</td>
</tr>
</tbody>
</table>

Table 1. Anti-retroviral agents used locally

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>Didanosine</th>
<th>Lamivudine</th>
<th>Stavudine</th>
<th>Tenofovir</th>
<th>Zidovudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Indinavir</td>
<td>Lopinavir/ritonavir</td>
<td>Ritonavir</td>
<td>Saquinavir</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Efavirenz</td>
<td>Nevirapine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
medication the patient is taking. Potential common and severe adverse effects that may occur, and actions to prevent or minimize their occurrence, are always discussed.

For example, a patient initiating therapy with zidovudine is extensively counseled on the gastrointestinal adverse effects that are likely to occur, especially during the first weeks of therapy. Such information can greatly increase adherence to the regimen.

Patients are also advised about proper storage of all medication, for example, ritonavir should be kept in a fridge especially in our hot summer months.

Potential for drug interactions

The importance of considering the potential for drug interactions in patients receiving HAART cannot be overemphasized. Drug–drug interactions may involve positive or negative interactions between antiretroviral agents or between these and drugs used to treat other coexistent conditions.

Clinically important interactions to consider when co-administering with antiretroviral drugs include interactions with the following drugs:

- methadone
- oral contraceptives (oestrogen-containing)
- anti-epileptics
- antidepressants
- lipid-lowering agents
- acid-reducing agents
- certain antimicrobials (e.g. clarithromycin, minocycline and fluconazole)
- some anti-arrhythmics
- tuberculosis therapy
- anti-cancer drugs
- immunosuppressant
- phosphodiesterase inhibitors
- anti-hepatitis C therapies

Many of these interactions are manageable (i.e. with/without dosage modifications, together with enhanced clinical vigilance) but in some cases (e.g. rifampicin and PIs) and didanosine and ribavirin (used in hepatitis C), the nature of the interaction is such that co-administration must be avoided.

The busy healthcare professional can turn to the local drug information pharmacists when seeking to check for potential drug interactions. In addition, the University of Liverpool’s comprehensive drug interaction website is an excellent and highly recommended resource.

Conclusion

With the dramatic decrease in opportunistic infections brought about by the standard use of HAART, the care of patients infected with HIV has largely been transferred to the outpatient setting. Consequently, community pharmacists will be increasingly involved in the outpatient care of HIV-infected patients by ensuring patient adherence to complex treatment regimens and providing pharmaceutical care.

References

CTF AD1 07/10 MT

Catafast®
Presentation: Catafast powder for oral solution in sachets of 10 mg diclofenac potassium. Indications: Short-term treatment of the following acute conditions: post-traumatic pain inflammation and swelling, e.g. due to sprains, post-operative pain, inflammation and swelling, e.g. following dental or orthopedic surgery. Acute non-inflammatory conditions in gynaecology e.g. primary dysmenorrhea or ectopic, menorrhagia, etc. When the treatment is expected to be of short duration, non-steroidal anti-inflammatory drugs, e.g. of diclofenac potassium, should be considered as an alternative to Catafast. Dosage: Adult and elderly patients: 10 to 20 mg daily in divided doses. Up to 150 mg daily in divided doses. For dysmenorrhea and gynaecological conditions, oral administration of 10 to 20 mg daily. In children: Up to 10 mg daily. Children and adolescents under 14 years of age: Avoid use. Contraindications: Acute or chronic peptic ulcer, bleeding or perforation, known hypersensitivity to diclofenac potassium or any of the excipients, serum bile acid or total bilirubin levels of at least 1.5 times the upper limit of normal. Patients who have had previous gastrointestinal bleeding or perforation, including patients with other gastrointestinal diseases, are at a higher risk of further bleeding events. May mask signs and symptoms of infection. Caution recommended in patients with symptoms of GI disease, asthma, seasickness, allergic rhinitis, chronic pulmonary diseases, chronic inflammation of the respiratory tract, elderly, or impaired hepatic function (including porphyria), ulcerative colitis or Crohn’s disease. Caution when used concomitantly with corticosteroids, anticoagulants, and antiepileptic drugs or herbal products. Caution white driving or using machines. Combined use with protective agents is to be considered in patients with history of peptic ulcers, and those requiring low dose aspirin. Monitoring of liver function and blood counts recommended during prolonged treatment. Monitoring of renal function recommended in patients with history of hypertension, impaired cardiac or renal function, excessive volume depletion, the elderly, patients treated with diuretics or drugs that impair renal function. Monitoring recommended in patients with defects of haemostasis. As Catafast contains a source of phenylalanine, patients with phenylketonuria, De-novo of severe fluid retention and oedema, very rarely reported serious skin reactions, some of them fatal (including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis). Discontinue at the first appearance. May be associated with a small increased risk of fatal arterial thrombotic events. Before treatment consider carefully patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and cerebrovascular disease, and before initiating further long-term treatment of patients with risk factors for cardiovascular disease. Pregnancy and lactation: Should not be used in the first and second trimester of pregnancy and by breast-feeding mothers. Not recommended for use in women attempting to conceive as it may impair fertility. Should not be used during breast-feeding in order to avoid undesirable effects in the infant. Interactions: Caution with concomitant use of diuretics and antihypertensives (e.g. beta blockers, ACE inhibitors, diuretics, other NSAIDs and corticosteroids, SSRIs. Monitoring recommended for patients receiving anticoagulants, antiparkinsonian agents as well as blood glucose or cholesterol controlling agents. Monitoring of serum lithium and digoxin levels recommended if used concomitantly. Decrease of diclofenac to be reduced in patients receiving ciclosporin. Interactions with concurrent use of gamma-aminobutyric acid. Adverse reactions: Common undesirable effects are: headache, dizziness, vertigo, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, diarrhoea, nausea, increased thirst. Rare undesirable effects are: hypotension, asthenia and anaphylactoid reactions (including hypertension and shock), oedema, anaemia, asthma (including anaphylaxis), gastritis, gastrointestinal haemorrage, haematoma, melanoma, haemorrhagic, gastrointestinal ulcer with or without bleeding or perforation, hepatitis, jaundice, liver dysfunction, urticaria, oedema. Very rare undesirable effects are: agranulocytosis, angioedema, angioedema (including blood oedema), dysphonia, dysuria, dyspepsia, edema, failure of adrenal cortical function, hypotension, anaphylactic shock, urticaria, oedema. Acute onset of the以上内容，您可以根据需要调整成适合的格式。
**DIAMICRON® MR 60 mg**
modified release tablets
Gliclazide

Evidence-based medicine including the ADVANCE study, the largest morbidity-mortality trial in diabetes

First scored modified release formulation allowing progressive titration

Efficient glycemic control with well proven tolerability and weight neutrality

Protective on the β-cell and the cardiovascular system

**Composition:**
Each modified-release tablet contains 60 mg of gliclazide.

**Indication:**
Type 2 diabetes.

**Dosage:**
One half to 2 tablets per day, ie, 30 to 120 mg as a single daily intake at breakfast time, including in elderly patients and those with mild to moderate renal failure. One DIAMICRON 60 mg modified release tablet is equivalent to two DIAMICRON 30 mg modified release tablets. The breakability of the DIAMICRON 60 mg modified release tablet enables flexibility of dosing to be achieved.

**Properties:**
Diamicron MR 60 mg is a sulfonylurea lowering blood glucose levels by stimulating insulin secretion thereby restoring the first peak of insulin secretion and increasing the second phase of insulin secretion in response to a meal or intake of glucose. Independent hemovascular properties. No active circulating metabolite.

**Contraindications:**
Hypersensitivity to sulfonylureas or sulfonamides, type 1 diabetes, diabetic precoma and coma, diabetic ketoacidosis, severe renal or hepatic insufficiency, treatment with miconazole, breast-feeding.

**Interactions:**
Increased risk of hypoglycemia with miconazole, phenylbutazone, alcohol, other antidiabetics, β-blockers, fluconazole, ACE inhibitors, H₂-receptor antagonists, MAOIs, sulfonamides, NSAIDs. Risk of hyperglycemia with danazol, chlorpromazine, glucocorticoids, β₂ agonists, ritodrine, salbutamol, terbutiline, anticoagulants. Adverse effects: Hypoglycemia, gastrointestinal disturbance; more rarely: skin and subcutaneous reactions, hematological disorders, hepato-biliary disorders, visual disorders.

**Overdosage:**
Possible severe hypoglycemia requiring urgent IV glucose and monitoring. Please refer to the complete summary of product characteristics for your country as variations may exist. LES LABORATOIRES SERVIER France, Correspondent: SERVIER INTERNATIONAL: 32, rue de Verdun, 92284 Suresnes Cedex, France. www.servier.com

**ADVANCEs in diabetes**