"Learning is about knowing how to find out what you don't know"

Editorial

The pharmacy profession is in a transition period as it is changing its focus from a product oriented to a patient-oriented one. Pharmacists world wide are embracing the philosophy of pharmaceutical care which advocates the rationalising of patients' drug therapy, educating patients about their medication and disease state and monitoring the outcomes of therapeutic plans. Contemporary pharmacy practice focuses on the patient and aims to optimise the interaction between the patient and drug product whilst encouraging the clinical aspects of patient management.

Studies carried out locally demonstrated that pharmacists, especially the younger forward-looking pharmacists, are willing to practice within the framework of this philosophy and those who have already done so locally proved to be as competent as their foreign counterparts. The Maltese general public has also expressed the desire for pharmacists to be more active in primary health care and are willing to participate in pharmaceutical care programmes.

The Malta College of Pharmacy Practice recognises the increasing importance of continuing education and continuing professional development in preparing pharmacists to practice within a pharmaceutical care framework. Over the past year a significant number of pharmacists practising in different fields have obtained postgraduate degrees both from local and foreign institutions. These pharmacists are voluntarily contributing to MCPP educational programmes and I would like to take this opportunity to offer them our sincere thanks. Their contribution to both undergraduate and postgraduate training, together with all the pharmacists having vast years of experience, continues to strengthen our profession.

Pharmacists who take an interest in the Malta College of Pharmacy Practice, by participating or through sponsorships, recognise the importance of continuing education. A recent editorial in the British Medical Journal cited the three most important words in education as being "I don't know" and stressed that in the modern world the most important thing was for a professional to be able to identify and admit to that which he does not know.

Respondents to our assessment questionnaire have clearly understood the meaning of the above statement and have offered their suggestions as to how we could do better in continuing education and for this we thank them.

The future of pharmacy in Malta is extremely encouraging. Not only are established members of the profession working hard to improve pharmacy locally, but are also leading members of international professional organisations. Undergraduate pharmacy students are also very active locally and internationally. Recently Ms. Sarah Caruana was elected vice-president of the European Pharmaceutical Students Association (EPSA).

The mission of the Malta College of Pharmacy Practice is to deliver a product which will help pharmacists increase their confidence in their field of practice. We look forward to the time when continuing professional development will be looked upon positively by all pharmacists. ✶

The Editorial Board would like to thank the pharmaceutical companies who have offered their sponsorship and made this edition of the Chronic*ill possible.

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Management of Migraine

Isabelle Farrugia B.Pharm.(Hons.),M.S.(UIC)

Completion of Assessment Questions following this article entitles members to one credit towards C.E. requirement.

Migraine is a complex neurovascular disease characterised by episodic attacks of severe headache accompanied by autonomic and neurological symptoms. Two types of migraine have been identified: (1) common migraine, or migraine without aura, occurring in about 70% of migraine patients (migraineurs); (2) classic migraine, or migraine with aura. In the latter case, aura symptoms are usually manifested as visual hallucinations such as flashing lights, zig-zag lines or blind spots, although sensory and motor dysfunction may also occasionally occur.

Migraineurs are defined as those individuals who have had at least two attacks of classic migraine, or at least five attacks of common migraine. Thus, any individual can suffer an isolated migraine attack without being a migraine patient. On the other hand, patients suffering from at least one attack during the previous year are termed active migraineurs. The epidemiology of migraine is similar across western countries and is highly dependent on age and gender. About 10% of the general population are active sufferers. However, several studies have shown that migraine is two to three times more prevalent in adult females than it is in adult males, with females in their 40's having the highest incidence. In active migraineurs, the median attack frequency is 1.5 per month and the median duration of attacks is just under one day although attacks lasting several days are known to occur. Thus, there is enormous variation from patient to patient as well as from attack to attack.

Migraine attacks can have profound effects on the day-to-day life and the well-being of the sufferer. Migraineurs suffering from frequent, debilitating attacks may have to absent themselves from work, or may experience reduced productivity even when attempting to perform normal daily activities. In addition, the impact of migraine stretches beyond the time of the actual attack, since some patients may have to curtail their activities to avoid situations that may trigger an attack. Reduction in the burden of migraine may be achieved through accurate diagnosis, assessment of the disability experienced by the individual and appropriate, well-executed treatment strategies. Moreover, the goal of the treatment should be not only to relieve pain, but to restore the patient's ability to function normally as rapidly as possible.

Diagnosis

Migraine is a common clinical disorder that continues to be highly under-recognized. Diagnosis is difficult because it is hard to elicit precise information from a patient who is trying to translate symptoms into words, the symptoms are somewhat similar to those of tension headaches, and the manifestation of attacks exhibits considerable inter- and intra-patient variability. The situation is further complicated by the fact that there are no biological markers to confirm diagnosis.

Based on the recommendations of the International Headache Society, a number of diagnostic criteria for migraine have been put forward (Table 1). These guidelines should all be taken into account when formulating a patient interview with the aim to obtain an accurate headache history of the sufferer. Such history-taking plays a key role in migraine diagnosis and should thoroughly address all the relevant criteria. During the interview, it is important to look out for and recognise certain patterns that are typical of migraine attacks. Thus, the patient should be questioned about:

- Family history of migraine
- Abatement of the headache with sleep
- Perimenstrual or periovulation timing of migraine attacks
- Stimulation of attack by sustained exertion
- Consistent precipitation of headaches by reliable triggers (Table 2).

Patient interview alone is not always sufficient to make a definite diagnosis of migraine. In such cases, it is essential for the patient to undergo a physical examination in order to eliminate the possibility that there is a more serious underlying cause of the headaches. Features which raise concern and which require immediate referral include:

1) a first severe headache of rapid onset
2) a marked change from a previously stable long-standing headache pattern

Table 1: Diagnostic criteria for Migraine

I. Migraine without aura

1) At least five attacks fulfilling criteria (2) to (4)
2) Headache attacks, untreated or unsuccessfully treated, lasting 4 to 72 hours
3) At least two of the following headache characteristics:
   a) unilateral location
   b) pulsation
   c) moderate to severe pain intensity (interferes with or prohibits daily activities)
   d) aggravation by motion (e.g. walking up stairs or similar routine activity)
4) At least one of the following associated symptoms:
   a) nausea and /or vomiting
   b) photophobia
   c) phonophobia
   d) osmophobia (aversion to odours)
5) No evidence of related organic disease

II. Migraine with aura

1) At least two attacks fulfilling criteria (2) to (5)
2) One or more fully reversible aura symptoms (usually manifested as visual disturbances)
3) At least one aura symptom develops gradually over > 4 minutes, or two or more symptoms develop in rapid succession
4) Duration of aura symptoms is 4 to 60 minutes
5) Headache follows aura within one hour, or begins before or simultaneously with aura

3) a new onset of headache after age 50

4) the precipitation of severe head pain by bending down, exertion or coughing

5) the presence of systemic symptoms such as fever, malaise, myalgia or weight loss.

Pharmacological Management of Migraine

Traditionally, the pharmacological management of migraine has focussed on two major approaches: symptomatic treatment and prophylactic therapy.

Symptomatic treatment

The objective of symptomatic treatment is to reduce the intensity and duration of pain and its associated symptoms, whilst optimising the patient's ability to function normally. Treatment of attacks generally involves the use of one or a combination of the following classes of drugs: simple analgesics, nonsteroidal anti-inflammatory drugs, antiemetics, narcotic analgesics, ergot derivatives and serotonin(1)-agonists. The choice of the medication depends on a number of patient factors (Table 3), and on the treatment strategy selected.

There are two major strategies for the treatment of migraine: step-care and stratified care. In step-care, all patients begin at the bottom of the therapeutic pyramid, starting with an inexpensive simple analgesic. After an appropriate trial, if treatment is unsuccessful, therapy is escalated until patients get the treatment that is successful. In stratified-care, the treatment of the patient is immediately matched with the severity of the condition. Thus, the patient's treatment needs must be identified by assessing the degree of disability experienced by the patient. In mild attacks, the patient can proceed with daily activities with only very minimal disruption; in moderate attacks, the patient experiences moderate impairment in normal activities; in severe attacks, the patient is unable to proceed with daily activities and experiences impaired efficiency in any capacity due severe discomfort; in ultra-severe cases, there is prolonged inability to function in any capacity.

Table 4 summarises the various drugs commonly used to treat mild and moderate attacks of migraine, and gives the initial dose that is generally used to treat migraine attacks in adult patients. Milder migraine headaches often respond to paracetamol or aspirin, but since peristalsis is often reduced during attacks the medications may fail to be sufficiently absorbed to be effective. Therefore, effervescent or dispersible formulations are preferable. Other non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen, mefenamic acid and tolfenamic acid have been used in the treatment of moderate migraine attacks, but their use may be restricted by their gastrointestinal side effects. In addition, oral anti-emetics, such as metoclopramide or prochlorperazine, are usually required as adjunctive therapy in order to relieve the symptoms of nausea associated with migraine. If vomiting is a problem,

Table 2: Precipitating factors of migraine attacks.

- Stress/strain/emotional disturbances
- Light stimulation/glare
- Lack of sleep, fatigue
- Excessive sleep
- Menstrual periods
- Fasting
- Alcohol
- Specific foods, such as chocolate, caffeine, aged cheeses
- Medications, such as oral contraceptives, nitroglycerine

Table 3: Factors influencing the choice of medication for acute migrane attacks

1) Severity of the attack (mild, moderate, severe)
2) Presence or absence of vomiting
3) Time from onset of pain to peak pain level
4) Comorbid medical conditions
5) Concomitant use of other medications
6) Adverse effects of the drug

domperidone or prochlorperazine may be administered rectally. Oral analgesic preparations containing metoclopramide constitute a convenient therapeutic alternative. Combination medications containing paracetamol or aspirin with codeine and/or caffeine may be used in patients who do not respond to simple analgesic therapy. However, such products should be used intermittantly and on a short-term basis in order to preclude rebound headache.

Oral ergotamine has been used in the management of migraine for many years. However, its use is limited by a number of factors. Firstly, it is associated with variable bioavailability due to erratic absorption. It has to be taken early during an attack to prevent vomiting and may actually sometimes cause nausea, vomiting, abdominal pain and muscular cramps as side effects. In addition, it cannot be prescribed in conjunction with commonly used prophylactic migraine treatments such as beta-blockers. To avoid habituation, the frequency of administration of ergotamine should be limited to no more than twice a month, treatment should not be repeated at intervals of less than four days and it should not be given prophylactically.

The newer triptan drugs, mainly sumatriptan and zolmitriptan, have today become the drugs of choice for the treatment of moderate migraine attacks which are unresponsive to NSAID therapy. These agents are highly selective serotonin 5HT1B/1D receptor agonists inhibiting cranial vasodilation and neurogenic inflammation. Zolmitriptan, which has improved oral bioavailability relative to sumatriptan, also crosses the blood brain barrier and has central effects, inhibiting the transmission of pain impulses. Unlike ergotamine, both sumatriptan and zolmitriptan are effective whether taken early or late after the onset of headache; however, sumatriptan is not effective during the aura phase preceding headache onset. Another advantage of the triptans over ergotamine is that they can be prescribed concomitantly with beta-blockers. However, the triptans should not be co-administered with ergotamine because of increased risk of vasospasm; in fact, ergotamine should be avoided for at least six hours after administration of either of the triptans, while sumatripan and zolmitriptan should be avoided for 24 hours and 6 hours respectively following the use of ergotamine. Side-effects associated with the triptans include nausea, dizziness, drowsiness, heat sensations, tingling, weakness, transient increases in blood pressure and heaviness, tightness or pressure in the neck, throat limbs or chest. Thus, these agents are contra-indicated in patients suffering from cardiac diseases or uncontrolled hypertension. Also, like ergotamine, they are contraindicated during pregnancy.

Severe migraine attacks may require parenteral administration of dihydroergotamine or triptan drugs, as well as adjunctive parenteral medications. Hence the patient should be referred to a physician's clinic or, in ultra-severe cases, to the hospital emergency department.

Prophylactic treatment

The main objective of prophylactic therapy is the reduction of the frequency, duration and intensity of attacks by at least 50% using the least amount of medication with the fewest side effects. Such therapy should be considered for patients suffering from two or more attacks per month, which do not respond to symptomatic treatment. When selecting a medication for prophylaxis, it is important to take into account the possible presence of co-morbid conditions and the drugs' side-effects. Agents used include:

1) beta-blockers without instrinsic sympathomimetic activity, such as atenolol, propranolol and metoprolol but not pindolol (contraindicated in patients with asthma, chronic obstructive pulmonary disease, peripheral vascular disease, heart failure and diabetes mellitus and in pregnancy)
2) tricyclic antidepressants, such as amitriptylene (contraindicated in patients with glaucoma and cardiac, kidney, liver, prostate or thyroid disease)
3) calcium-channel blockers, such as verapamil, nifedipine and flunarizine (contraindicated in

Table 4: Commonly used medications for the treatment of migraine of different severity.

Drug	Proprietary name	Initial Oral Adult Dose
I. Mild attacks		
Paracetamol	Panadol® (Sterling Health)	1000 mg
Aspirin	Aspro® (Roche)	500-1000 mg
Ibuprofen	Nurofen® (Crookes Healthcare)	400 mg
Naproxen sodium	Naprosyn® (Roche)	500 mg
Metoclopramide	Maxolon® (SmithKline Beecham)	10 mg
Domperidone	Motilium® (Janssen)	20 mg
Dimenhydrinate	Dramamine® (Searle)	100 mg
II. Moderate attacks		
Ibuprofen	Nurofen® (Crookes Healthcare)	400 mg
Naproxen sodium	Naprosyn® (Roche)	500mg
Mefenamic acid	Ponstan® (Parke-Davies)	500 mg
Tolfenamic acid	Clotam® (GEA Ltd.)	200 mg
Ergotamine	Migril ® (GlaxoWellcome)	1-2 mg
Sumatriptan	Imigran® (GlaxoWellcome)	50-100 mg
Zolmitriptan	Zomig® (Zeneca)	2.5-5 mg
Combination drugs:		
Paracetamol+ codeine+caffeine	Solpadeine® (Smithkline Beecham)	2 tablets
Paracetamol+codeine	Migraleve® (Pfizer)	2 tablets
Aspirin+codeine	Codis® (Reckitt & Colman)	2 tablets

pregnancy, and in patients with hypotension, arrhythmias, congestive heart failure)

4) pizotifen, which however may cause fatigue, drowsiness and weight gain

5) sodium valproate, which however has occasionally been associated with severe hepatic and pancreatic toxicity

6) NSAIDs, which however should only be used intermittently, for example to prevent perimenstrual attacks, in view of their gastrointestinal side effects.

Except in the most resistant cases, it is recommendable to use only a single prophylactic agent at any time. Prophylactic therapy should not be expected to work immediately and may take several weeks before an effect is observed. Treatment should be started at a low dose, and the dosage subsequently increased to the maximally effective tolerable dose. The therapy should be continued for an adequate period, and then withdrawn gradually to minimise the risk of rebound headaches.

Conclusion

Pharmacists are in an excellent position to educate patients on the nature of migraine and its management and hence improve patient compliance. They may help patients to understand the actions of their medications and the possible adverse effects, drug interactions and contraindications (e.g. pregnancy) associated with their therapy. They may assess the degree of patient compliance to prescribed prophylactic medications. Pharmacists may also offer advice to patients on non-drug therapies such as relaxation techniques. Another important area is the identification and avoidance of triggering factors including specific foods, and hence the provision of dietary advice.

These factors make the pharmacist a key role-player in the provision of pharmaceutical care in the prevention and treatment of migraine. ✶

Completion of Assessment Questions following this article entitles members to one credit towards C.E. requirement.

Bibliography

Deleu, D., Hanssens, F., and Worthing, E. (1998) Symptomatic and prophylactic treatment of migraine - a critical reappraisal. Clinical Neuropharmacology, 21: 267-279.

Doughty, M., and Lyle, W. (1995) Medications used to prevent migraine headaches and their potential ocular adverse effects. Optometry and Vision Science, 72: 879-891.

Ferrari, M. (1998) Migraine. The Lancet, 351: 1043-1051.

Goadsby, P., and Olesen, J. (1997) Increasing the options for effective migraine management. Neuralgia, 48: S1-S3.

Headache Classification Committee of the International Headache Society. (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgia and facial pain. Neuralgia, 8: 1-96.

Lipton, R., and Stewart, W. (1997) Clinical applications of zolmitriptan (Zomig™, 311C90). Cephalgia, 17: 53-59.

Maizels, M. (1998) The clinician's approach to the management of headache. Western Journal of Medicine, 168: 203-212.

Pryse-phillips, W., Dodick, D., Edmeads, J., Gawel, M., Nelson, R., Purdy, A., Robinson, G., Stirling, D., and Worthington I. (1997) Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Medical Association Journal, 156: 1273-1287.

Zagami, A. (1997) 311C90: Long-term efficacy and tolerability profile for the acute treatment of migraine. Neuralgia, 48: S1-S3.

Management of Migraine

Select only ONE option in each question by ticking the respective box on the Response Sheet (page 39).

Assessment Questions:

1. Which of the following symptoms is not normally associated with migraine?
   a) headache
   b) nausea
   c) vomiting
   d) diarrhoea

2. In migraine, head pain is not accompanied by:
   a) photophobia
   b) phonophobia
   c) xenophobia
   d) osmophobia

3. Migraineurs are defined as those individuals who have had at least
   a) two
   b) three
   c) four
   d) five
   attacks of common migraine.

4. The highest incidence of migraine occurs in
   a) young boys
   b) young girls
   c) adult females
   d) adult males

5. What is the normal initial dose of zolmitriptan in the treatment of migraine in adults?
   a) 0.25 mg
   b) 2.5 mg
   c) 25 mg
   d) 250 mg

6. What is the normal initial dose of sumatriptan in the treatment of migraine in adults?
   a) 0.1 mg
   b) 1 mg
   c) 10 mg
   d) 100 mg

7. Which of the following drugs is used in the prevention of migraine attacks?
   a) amitriptylene
   b) propranolol
   c) pizotifen
   d) all of the above

8. Which of the following beta-blockers cannot used as a migraine prophylactic agent?
   a) atenolol
   b) pindolol
   c) propranolol
   d) metoprolol

9. Which of the following drugs can be used concomitantly with beta-blockers?
   a) zolmitriptan
   b) ergotamine
   c) verapamil
   d) dihydroergotamine

10. Which of the following foods is known to be a migraine triggering factor?
    a) carrots
    b) cheese
    c) potato
    d) rice

11. A migraine attack may be triggered by:
    a) stress
    b) excessive sleep
    c) insufficient sleep
    d) all of the above

12. Which of the following anti-emetics is generally administered rectally in migraine patients experiencing vomiting?
    a) metoclopramide
    b) domperidone
    c) dimenhydrinate
    d) none of the above

13. Which of the following drugs is used in the treatment of migraine attacks?
    a) nalidixic acid
    b) tolfenamic acid
    c) ascorbic acid
    d) none of the above

14. Which of the following drugs would be preferable in the first-line treatment of a mild migraine attack in an asthmatic individual?
    a) ibuprofen
    b) paracetamol
    c) atenolol
    d) naproxen

15. Which of the following drugs can be used to treat migraine in pregnant women?
    a) sumatriptan
    b) ergotamine
    c) zolmitriptan
    d) none of the above

16. Which of the following factors should be taken into account when selecting the appropriate antimigraine therapy for a patient?
    a) severity of the attack
    b) presence or absence of vomiting
    c) presence of concomitant medical conditions
    d) all of the above

17. What is the main reason for combination products containing NSAIDs to be used only intermittantly?
    a) prolonged use may give rise to rebound headache
    b) the patient may become tolerant to the medication
    c) the patient may develop an allergic reaction to the drug
    d) the high cost associated with continuous use of such products

18. Which of the following classes of drugs are not used in the management of migraine?
    a) beta-receptor blocking agents
    b) histamine-receptor agonists
    c) serotonin(1)-receptor agonists
    d) none of the above

19. Which of the following symptoms is not a common adverse effect associated with the triptan drugs?
    a) drowsiness
    b) warm sensation
    c) nausea
    d) skin rash

20. Amitriptylene should not be used to prevent migraine in patients with
    a) cardiac disease
    b) thyroid disease
    c) glaucoma
    d) all of the above

The Treatment of Asthma with Leukotriene Receptor Antagonists

Maria Cordina B.Pharm.(Hons.), Ph.D. (QUB)

Completion of Assessment Questions following this article entitles members to one credit towards C.E. requirement.

Over the past three decades the pharmacotherapy of asthma has been based on glucocorticoids, ß$_2$ agonists and theophyllines. Research conducted over the past 10 years has led to greater understanding of the cellular and molecular basis of asthma, particularly the role of the underlying inflammatory process.

Both national and international guidelines stress the importance of switching off the inflammatory cascade (Figure 1). Glucocorticoids are the most effective anti-inflammatory agents available and in many countries, including Malta, they are used as first line treatment. However, despite their proven safety and efficacy, there are still a number of patients whose asthma is not adequately controlled and as a consequence have a poor quality of life.

The search for alternative pharmacological agents that target airway inflammation and ease the problem of compliance has led to a novel class of non-steroidal anti-asthma drugs which are effective over a wide range of asthma severity, have a high therapeutic index, are orally active and have a once daily or twice daily regimen. Leukotriene receptor antagonists are a hybrid between a preventer of inflammation (antagonism of inflammatory activities of leukotrienes) and bronchodilating reliever (antagonism of leukotriene induced smooth muscle bronchoconstriction). Currently available on the local market is zafirlukast (Accolate®, Zeneca) which is a cysteinyl leukotriene antagonist. Another drug within this class, however not as yet available locally, is montelukast (Singulair®, Merck).

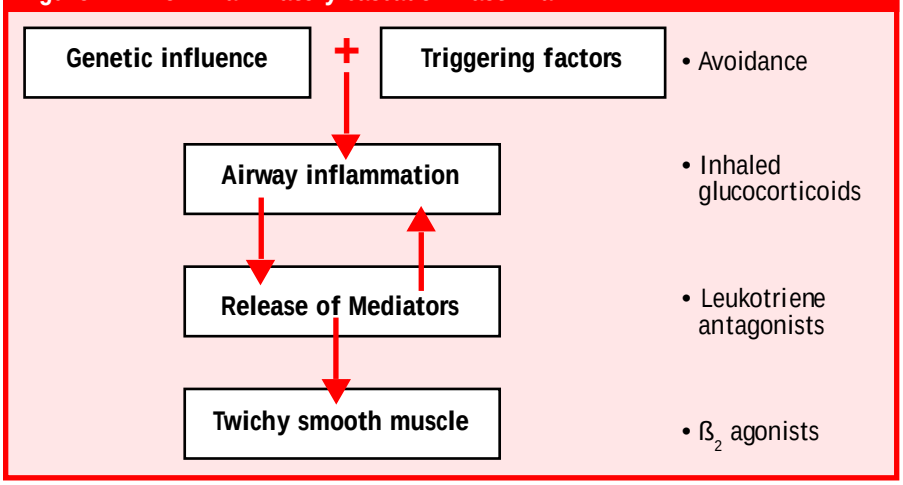
What are leukotrienes?

Leukotrienes are a group of arachidonic acid derivatives that are produced during asthmatic reactions by cells involved in the pathogenesis of asthma and other inflammatory diseases. The cysteinyl leukotrienes C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4) are important mediators of inflammation. They are formed in many cells including mast cells and eosinophils and are potent inducers of bronchoconstriction, plasma exudation and mucus production.

How do the new anti-leukotriene drugs work?

There are currently four classes of anti-asthma and anti-inflammatory drugs which interfere with leukotriene synthesis or activity which are under development as seen in Figure 2. These are 5-lipoxygenase inhibitors and 5-lipoxygenase activating protein (FLAP) inhibitors which block the synthesis of cysteinyl leukotrienes and the

Figure 1 The inflammatory cascade in asthma



leukotriene B_4 (LTB_4). The third class are competitive antagonists of LTB_4. The drugs which are currently available in Malta and the UK are those of the 4th class and act by competitively blocking the activity of cysteinyl leukotrienes at the LTD_4 receptor. They are termed cysteinyl leukotriene receptor antagonists.

When should leukotriene receptor antagonists be used?

The local guidelines on the management of asthma issued by the Malta Lung Study Group do not mention the use of leukotriene receptor antagonists. However, these guidelines are in the process of being revised. The position of these drugs in the international guidelines is still unclear due to the lack of published data at the time of drawing up these guidelines. It is debatable whether these drugs should be used as first-line preventive monotherapy instead of low dose inhaled corticosteroids in patients with mild persistent asthma or as an alternative to long-acting bronchodilators, i.e. second-line therapy, in addition to inhaled corticosteroids in patients with moderate to severe persistent asthma.

It is important to note that leukotriene receptor antagonists should be taken on a regular basis to achieve benefit, even during symptom free periods and should normally be continued during acute exacerbations of asthma. However, they are not indicted to relieve an attack of acute severe asthma.

In the UK, zafirlukast is licensed for use in patients aged 12 years and over. It may be used as first line therapy instead of inhaled corticosteroids in mild persistent asthma. Montelukast is licensed in patients aged 6 and over as second line asthma treatment in combination with inhaled corticosteroids and as monotherapy in exercise induced asthma.

Clinical considerations

Zafirlukast and montelukast both achieve peak plasma concentrations approximately 3 hours after oral administration. There is a 40% decrease in the bioavailability of zafirlukast when taken with food; it is therefore recommended that the tablets should not be taken with food as this could lead to a decreased pharmacological response. Co-adminstration of zafirlukast with erythromycin, theophylline or terfenadine results in a decrease in the plasma concentration of zafirlukast, while an increase results when it is co-administered with aspirin. In smokers the clearance of zafirlukast may be increased by about 20%. Prescribing information regarding the use of zafirlukast states that the safety of this drug in pregnancy has not been established and since it is excreted in breast milk it should not be administered to lactating mothers.

The literature suggests that leukotriene receptor antagonists may be of particular use in:

- **exercise induced asthma**
- **asthmatics who are intolerant to aspirin and other non-steroidal anti- inflammatory drugs**
- **nocturnal asthma**
- **asthmatics who concomitantly present with allergic rhinitis.**

Official montelukast prescribing information advises that the use of montelukast is avoided in pregnancy and lactation unless essential.

Conclusion

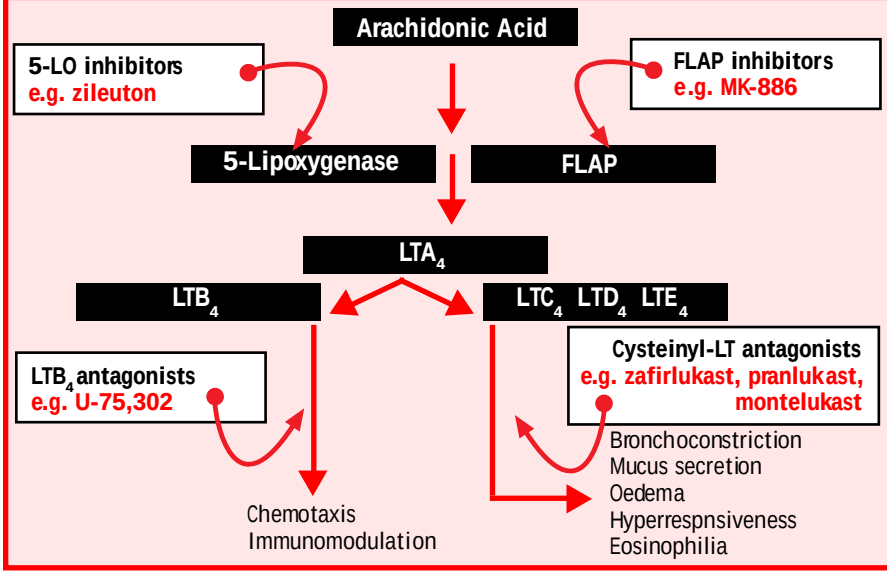
Leukotriene receptor antagonists represent an important advance in asthma therapy. They are active over a wide range of asthma severity and have both an anti-inflammatory and a bronchodilator property. They are active orally, therefore overcoming the potential problems with compliance when using inhalers.

They also act within the first 24 hours while inhaled corticosteroids take a much longer time to achieve maximal

Table 1 Leukotriene Receptor Antagonists

Generic	Propriety	Oral dose	Other information
Zafirlucast	Accolate (Zeneca)	20 mg bd	Take 1hr before or 2hr after eating.
Montelukast	Singulair (Merck)	Adults: 10 mg at night Paed: (6-12yr): 5 mg at night	Paediatric dose available as chewable tablets.

Figure 2 The four groups of anti-asthma and anti-inflammatory drugs directed against LT synthesis and activity



response. However, when compared to inhaled beclomethosone 400 micrograms daily both the above mentioned drugs appear to be less effective in mild to moderate asthmatics. They are comparable in cost to long acting $ß_2$ agonists but more expensive than low dose inhaled steroids.

While further long term studies are required to determine the position of these drugs in asthma treatment guidelines, they provide oral, safe and effective therapy. ✶

Bibliography

Dahlen, S-E, Bjork, J., Hedqvist, P., et al. (1981) Leukotrienes promote plasma leakage and leukocyte adhesion in post-capillary venules: in vivo effects with relevance to the acute inflammatory response. Proceedings of The National Academy of Sciences USA, 78: 3887-3891.-

Dahlen, S-E, Hedqvist, P., Hammarstrom, S. and Samuelsson, B. (1980) Leukotrienes are potent constrictors of human bronchi. Nature, 288: 484-486.

Drazen, J.M., Israel, E. and O'Byrne, P.M. (1999) Treatment of asthma with drugs modifying the Leukotriene pathway. New England Journal of Medicine, 340: 197-206.

Geddes, D. (1992) Inhaled corticosteroids: benefits and risks. Thorax, 47:404-407.

Holgate, S.T., Bradding, B.M. and Sampson, A.P. (1996) Leukotriene antagonists and synthises inhibitors: new directions in asthma therapy. Journal of Allergy and Clinical Immunology, 98:1-13.

Lipworth, B.J. (1999) Leoukotriene-receptor antagonists. Lancet, 353:57-62.

Lipworth, B.J. (1999) Modern treatment of modern asthma. British Medical Journal, 318: 380-384.

Malta Lung Study Group. (1998) Asthma: Guidelines for Management. Department of Health, Malta.

Marom, Z., Shelhamer, J.H., Bach, M.K., Morton, D.K. and Kaliner, M. (1982) Slow-reacting substances, leukotrienes C4, D4 and E4. Proceedings of The National Academy of Sciences USA. American Review of Respiratory Disease, 126: 449-451.

National Asthma Education and Prevention Programme. (1997) Expert panel report II:. Guidelines for the diagnosis and management of asthma. Bethesda: National Institutes of Health Publication, 97-4051.

Taylor, I.K. (1995) Cysteinyl Leukotrienes in asthma: current state of therapeutic evaluation. Thorax, 50:1005-1010.

The Treatment of Asthma with Leukotriene Receptor Antagonists

Select only ONE option in each question by ticking the respective box on the Response Sheet (page 39).

Assessment Questions:

1. The inflammatory process in asthma is:

a. of secondary importance
b the main pathological process in asthma
c the target of all anti-asthma drugs
d all of the above.

2. Which of the following statements is true?

a. Leukotrienes are arachidonic acid derivatives
b. Leukotrienes are only involved in the pathogenesis of asthma
c. Leukotrienes are only produced in mast cells
d. Leukotrienes are not involved in mucus production.

3. Leukotriene receptor antagonists are
a. non-steroidal drugs
b. enhance the inflammatory process
c. steroidal drugs
d a combination of answers a and b.

4. Leukotriene receptor antagonists
a. have anti-inflammatory activities
b. act in the same way as $ß_2$ agonists
c. have bronchodilating effects
d. a combination of answers a and c.

5. Leukotriene receptor antagonists currently available on the local market are
a. pranlukast
b. montelukast
c. zafirlukast
d. salbutamol

6. The cysteinyl leukotriene receptor antagonists act by
a reducing arachidonic production
b. reducing FLAP synthises
c. competing with the LTB_4 receptor
d. blocking the LTD_4 receptor.

7. Which of the following statements is true
a. an example of a 5-lipoxygenase inhibitor is montelukast
b. LTD4 is a not cysteinyl leukotriene
c. zafirlukast is a cysteinyl leukotriene receptor antagonist
d. cysteinyl leukotriene receptor antagonists are ineffective if taken with inhaled corticosteroids.

8. The recommended use of cysteinyl leukotriene receptor antagonists
a. as reliever therapy i.e. instead of short acting (2 agonists
b. instead of oral prednisolone
c. instead of inhaled steroids in mild persistent asthma
d. instead of nebulised therapy.

9. Zafrilukast is also licensed for use in
a. COPD
b. bronchitis
c. emphysema
d. none of the above.

10. Leukotriene receptor antagonists are of particular use in
a. aspirin sensitive asthmatics
b. asthmatics allergic to salbutamol
c. persons presenting with occupational asthma
d. none of the above.

11. Which of the following statements is false?
a. cortocosteriods are the most effective anti-inflammatory agents available
b. zafirlukast is the only cysteinyl leukotriene receptor antagonist available locally
c. montelukast is licensed for use in the UK
d. leukotriene receptor antagonists only have a bronchodilating effect.

12. Which of the following statements is true?
a. zafirlukast is licensed only for use in patients over 12 years of age.
b. zafirlukast is also licensed for use in children over 6 years of age
c. montelukast is of no use in exercise induced asthma
d. montelukast has a low therapeutic index.

13. Zafirlukast and montelukast achieve peak plasma concentrations how long after administration?
a. after 30 minutes
b. after 1 hour when taken with food
c. after 3 hours
d. none of the above

14. Zafirlukast is available as
a. an inhaler
b. nebuliser solution
c a tablet
d. a combination of answers a and b.

15. Montelukast is available as
a. chewable tablets for children
b. suspension
c. tablets for adults
d. a combination of answers a and c.

16. The dosage regimen for zafirlukast is
a. 20 mg bd. with food
b. 20 mg bd. 2 hours after food
c. 20 mg bd. 1 hour before food
d. a combination of answers b and c

17. The use of cysteinyl leukotriene receptor antagonists in pregnancy and lactation
a. is absolutely safe.
b. is recommended after the 2nd trimester
c. is not recommended
d. none of the above.

18. One of the major advantages of cysteinyl leukotriene receptor antagonists is
a. their low cost
b. that they over come the problem of compliance with inhalers
c. that they can safely be used in children of all ages
d. that they have no side effects.

19. When used in mild to moderate asthma leukotriene receptor antagonists
a. are the most effective anti-inflammatory agents
b. are less effective than inhaled beclomethosone 400(g daily
c. are just as effective as any anti-asthma drug
d. are of no use.

20. Which of the following statements is true?
a. cysteinyl leukotriene receptor antagonists should be taken on a prn basis
b. cysteinyl leukotriene receptor antagonists should be taken on a regular basis
c. cysteinyl leukotriene receptor antagonists should only be taken in conjunction with salmeterol
d. cysteinyl leukotriene receptor antagonists should not be taken if cough is present.

"To loose one's health renders science null, art inglorious, strenght effortless, wealth useless and eloquence powerless."

Adversus Ethicus

Health Promotion and the Community Pharmacist

Maria Ellul B. Pharm.(Hons.) M.Sc.(Aber.) FRSH RPH Nut.
Director, Health Promotion Department

What is Health Promotion?

Health is a precondition for well-being and quality of life. It is also a basic human right and is essential for social and economic development. Increasingly, health promotion is being recognised as an essential element of health development. It is a process of enabling people to increase control over, and to improve, their health whether it is physical, mental, emotional or spiritual.

The Jakarta Declaration (1997) states that health promotion, through investment and action, has a marked impact on the determinants of health so as to create the greatest health gain for people, to contribute significantly to the reduction of inequities in health, to further human rights, and to build social capital.

The ultimate goal is to increase health expectancy, and to narrow the gap in health expectancy between countries and groups.

Health Promotion makes a Difference

Research and case studies from around the world provide convincing evidence that health promotion is effective. Health promotion strategies can change lifestyles and have an impact on the social, economic and environmental conditions that determine health. It is nowadays no longer sufficient to talk of health education but to invest in health promotion. It is a practical approach to achieving greater equity in health.

Health promotion is carried out by and with people, not on or to people. It improves both the ability of individual to take action, and the capacity of groups, organisations or communities to influence the determinants of health. In this way, health promotion increases community capacity and empowers individuals.

The Pharmacy as a Setting for Health Promotion

All health professionals are in an opportune position to enable their clients to make healthier choices and the pharmacist is no exception. Pharmacists are increasingly ready to provide health advice. Pharmacists mostly deal with customers that are not ill. They may be shopping for toiletries or picking up a prescription for someone else. But this visit presents an opportunity to provide customers with healthier information.

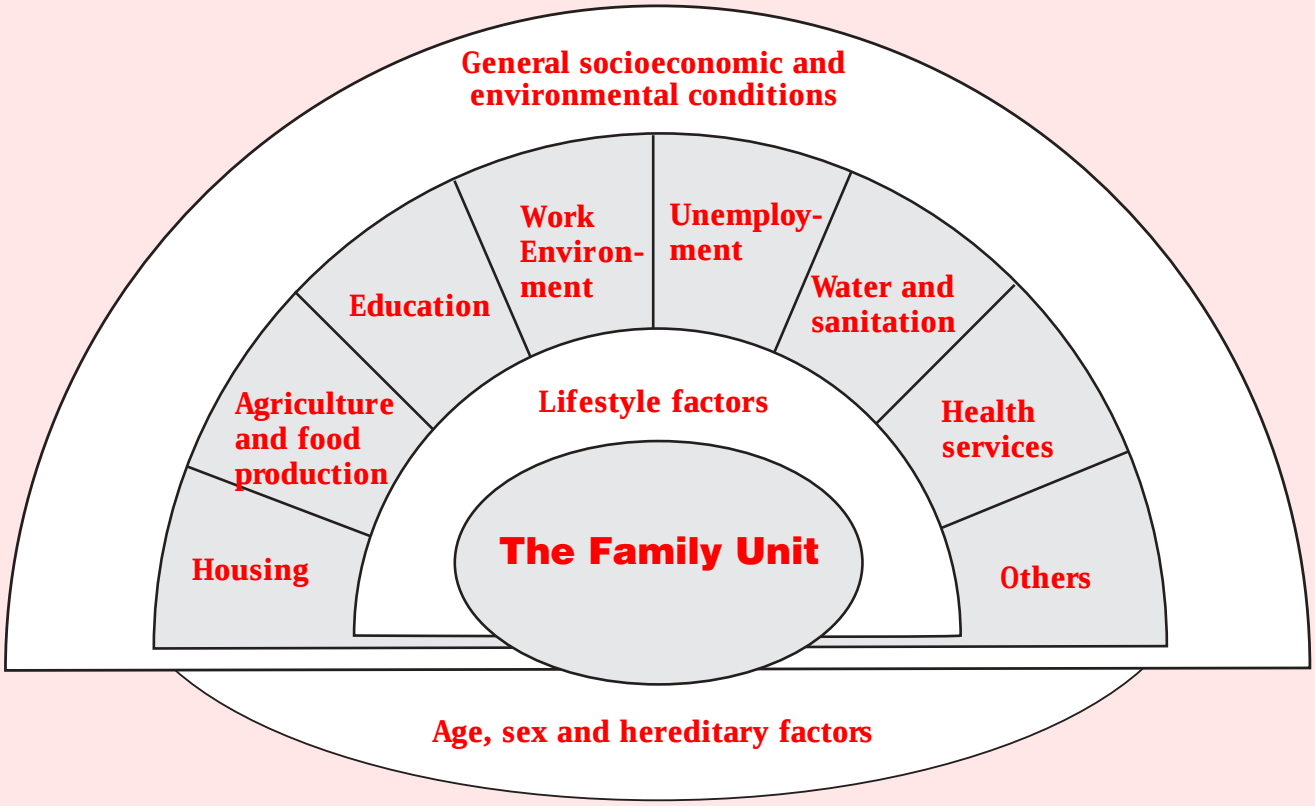
In the UK the Pharmacy Healthcare Scheme (PHS), an agency that promotes health education in the pharmacy setting, states that the accessibility of the pharmacist in the community and the potential contact for those not visiting the GP make the pharmacist a highly valued member of the healthcare team.

All pharmacists should be involved in encouraging healthy behaviour. This can be done by setting aside space for health promotion literature, responding to the requests for advice and providing simple health promotion advice when giving out prescriptions, making sales and responding to symptoms. It is also worthwhile to seek opportunities to promote health in the pharmacy e.g. prohibition of smoking; encouraging breast-feeding on-site; advocating a non-medicinal approach when applicable to problems easily solved by life-style changes. In this way pharmacists may identify the stage of change the person is at and offer advice and ongoing support. This is most appropriate in the case of smokers seeking advice on cessation techniques as well as in the management of overweight individuals. Both scenarios are very relevant to the local scene and involve stages of behaviour change in a person's lifestyle.

The EU also stresses that pharmacists may get involved in advising customers on appropriate off-the-self medicine. Pharmacists may also provide advice on when it would be appropriate to seek the doctor's advice. Other issues concern the side-effects and contra-indications of prescribed medications and how to take these medications effectively. They also provide advice on when it would be appropriate to seek the doctor's advice.

By providing health promotion, the role of the pharmacist is broadened further and adds to the approach of

Figure 1 Main Determinants of Health



Source: Dahlgren, G. & Whitehead, M. **Policies and strategies to promote social equity in health.** Stockholm, Institute for Future Studies, 1991.

holistic health as defined in the pharmacy setting.

Health Promotion at Undergraduate Level

It is therefore crucial that health promotion becomes part of the undergraduate pharmacy curriculum. This should be a natural development in the preparation of students leading to this profession. Future pharmacists need to understand the principles of health promotion if they are to be in line with other health professions where this training is already being done. Such training would facilitate pharmacists in becoming advocates of health promotion.

In the future all health professions, including the medical one, will require a good foundation of health promotion if they are to deliver good quality care. The World Health Organisation is continually stressing that developed countries need to build multisectoral strategies to promote health in all settings whether in the community, school, hospitals, pharmacies and workplaces.

Conclusions

The Health Promotion Department in Malta keeps the community pharmacist updated on recent campaigns and publications available to the public through mail shots. The pharmacist however, also needs to act provocatively to remain abreast on such issues and to encourage the community it serves in choosing healthier lifestyles by learning skills that enable them to take control of their health.

Through alliance building with the community pharmacist, it is hoped that the future initiatives by the Health Promotion Department will find a firm standing in our towns and villages. ✶

Bibliography

Jakarata Declaration 1997

Community Pharmacists-High Street Help. Marc Beishon. Healthlines Magazine, May 1999

Health Promotion: & The Community Practice. Kemm & Close. 1995

Health Promotion & The Community Pharmacist. Health Education Authority. 1994

Publications

available from the Health Promotion Department

LEAFLETS AND BOOKLETS

- HEALTH PROMOTION DEPARTMENT
  Mission statement & Services

SEXUALITY & HIV/AISDS

- WHILE YOU'RE IN MALTA & GOZO
  The traveller's Guide to Healthy Sex Life
  (Italian, German, French, Arabic, English)
- HIV & AIDS This information can save your life
- SAHHTEK HIJA HAJTEK, HU HSIEBA

WOMAN'S HEALTH

- IL-MENOPAWSA
- IL-HYSTERECTOMY
- IL-PERIOD
- L-IPPJANAR TAL-FAMILJA
- KIF THARES SIDREK
- BREAST FEEDING SUCCESSFULLY

GENERAL HEALTH

- IS-SAHHA MENTALI
- IS-SAHHA MENTAL Informazzjoni ghall-familjari u hbieb ta' nies bi problemi mentali.
- CYSTITIS
- TUBERCULOSIS
- EPILEPSY
- ASTHMA

ACCIDENT PREVENTION

- AHSEB MINN QABEL L-Incidenti jistghu jigu evitati jekk nahsbu minn

SMOKING CESSATION

- TAF X'JAGHMILLEK IT-TIPJIP ?
- TRID TIEQAF TPEJEP? ARA KIF
- TPEJJIPX (Mela inti trid tpejjep?)
- MALTA'S SMOKE-FREE ZONE
  Smoke-free restaurants.

HEALTHY EATING & WEIGHT MANAGEMENT

- KUL GHAL QALBEK
  Fibre; Ix-xahmijiet u zjut; Il-verita' qarsa fuq iz-zokkor; u Kul ikel tajjeb u skansa l-mard.
- GUIDELINES TO INFANT FEEDING
- HEALTHY EATING FOR SCHOOL CHILDREN
- IKEL BNIN - IL-MOD MEDITERRANJU!
- KULL 5 KULJUM Kampanja favur il-konsum tal- haxix u l-frott.
- POSTCARDS - KALCJU, HADID u l-FOLIC ACID.
- IKEL BNIN WARA S-SITTIN
- GWIDA TA' L-IKEL BIEX TIKKONTROLLA IX-XAHAM FID-DEMM
- GWIDA TA' L-IKEL SABIEX TIKKONTROLLA L- PRESSJONI GHOLJA
- GWIDA GHAL- DIETA BILANCJATA SABIEX TONQOS MILL-PIZ
- PARIR BIEX TNAQQAS IL-PIZ ZEJJED
- YOUR HEALTHY GUIDE TO LOSING WEIGHT

The Antiplatelet Activity of Aspirin

Claude A. Farrugia B.Pharm.(Hons.), Ph.D.(UIC)

Completion of Assessment Questions following this article entitles members to one credit towards C.E. requirement.

The synthesis of aspirin in the late nineteenth century marked the development of what was to become the most widely used household analgesic in the twentieth century. However, with the increased understanding of the major role of platelets in vascular occlusion over the last ten years, the importance of aspirin as an antiplatelet drug and, consequently, its applications in reducing the risks of thrombotic vascular events, have received major attention.

Pharmacology and Mechanism of Action

Aspirin, otherwise known as acetylsalicylic acid, acts by acetylation of the two isoenzyme forms of prostaglandin G/H synthase. This results in the irreversible inactivation of the cyclooxygenase activity of this enzyme, preventing the conversion of arachidonic acid to prostaglandin G_2, and consequently decreasing biosynthesis of prostaglandin H_2 and thromboxane A_2. The type one isoenzyme of prostaglandin G/H synthase is constitutively expressed in platelets, where synthesis and release of thromboxane A_2 occurs in response to a variety of stimuli, resulting in irreversible platelet aggregation. Platelets, platelet products and thombosis play important roles in the occurrence of acute occlusive vascular events, including myocardial infarction (MI) and ischemic stroke, since the disruption of platelet- and fibrin-rich atheroschlerotic plaque may be followed by aggressive platelet deposition and, ultimately the development of a thrombus that can precipitate an acute occlusive event. The decreased platelet aggregation caused by aspirin is the most plausible mechanism for the cardioprotective effects of this drug.

Dose-dependant inhibition of platelet cyclooxygenase activity occurs with single aspirin oral doses of 5 to 100 mg, with the latter dose resulting in practically total suppression of thromboxane A_2 biosynthesis. The onset of activity of the drug is extremely rapid and unrelated to systemic bioavailability, probably due to platelet prostaglandin synthase suppression in the portal circulation. Furthermore, since platelets lack the intracellular machinery necessary to regenerate prostaglandin synthase, recovery from the effects of aspirin is related to platelet turnover (7 to 10 days), with repeated doses exerting a cumulative effect. This accounts for the fact that a drug with a half-life of 20 minutes is effective even when administered once daily.

Primary Prevention of Occlusive Cardiovascular Disease

The efficacy of aspirin at preventing important cardiovascular events, chiefly myocardial infaction, stroke and cardiovascular mortality has been assessed in healthy subjects and subjects with stable chronic angina. Also, since patients with insulin-dependent and non-insulin-dependent diabetes mellitus, and hypertensive individuals have an increased risk of cardiovascular complications, including myocardial infarction and stroke, these categories of patients have also received attention in studies assessing the antiplatelet activity of aspirin. The results of these studies are summarised in Table 1.

Despite the significant reduction in MI incidence noted in the Physicians' Health Study, the benefit of aspirin in healthy individuals appears to be minor, given the very low absolute risk of cardiovascular events in healthy individuals (only 5% had an event during approximately 5 years of follow-up). However, in patients with an existing medical condition predisposing to a cardiovascular event, the use of aspirin appeared to have significant benefits. In particular, in the medium-risk population investigated in the Swedish Angina Pectoris Aspirin Trial, the results suggested the potential to prevent 51 important cardiovascular events in 1000 patients over four years, an absolute benefit at least tenfold greater than that obtained in the British Doctors' Trial and the Physicians' Health Study. Similar benefits were also observed in hypertensive patients.

Secondary Prevention of Occlusive Vascular Disease

The benefits afforded by aspirin in the prevention of secondary cardiovascular events supercede those

Table 1: Trials of Aspirin in the Primary Prevention of Occlusive Cardiovascular Disease.

Study	Type of Subjects	Number of Patients	Aspirin Dose	Outcome
British Doctors' Trial	Healthy males, 50-78 yrs old	5,139	500 mg daily vs placebo	No significant difference
Physicians' Health Study (USA)	Healthy males, 40-84 yrs old	22,071	325 mg every other day vs placebo	39% decrease in MI; 18% decrease in important cardiovascular events
Swedish Angina Pectoris Aspirin Trial	Patients with chronic stable angina without previous MI	2,035	75 mg daily vs placebo	34% decrease in MI and sudden death occurrence; 22 - 32% decrease in secondary outcomes
Early Treatment Diabetic Retinopathy Study	Patients with diabetes, 49% of whom with cardiovascular disease history	3,711	650 mg daily vs placebo	28% decrease in MI, 16% increase in stroke, 18% decrease in important cardiovascular events
Hypertension Optimal Treatment Trial	Hypertensive patients (diastolic BP100-115 mmHg), 50-80 yrs old	18,790	75 mg daily vs placebo	36% decrease in MI, 15% decrease in major cardiovascular events

for primary events. The drug remains the standard antiplatelet reference compound for secondary prevention of myocardial infarction, cardiovascular-associated death, and stroke. To this date, no other antiplatelet agent can compete with aspirin in these indications. Three main areas, in increasing order of severity, have been identified where the antiplatelet activity of aspirin plays a significant role in preventing secondary cardiovascular events. These are:

a) unstable angina and nonacute myocardial infarction

b) suspected acute evolving myocardial infarction and acute nonfatal myocardial infarction, and

c) transient cerebral ischaemia and stroke.

Three major studies all established that the administration of aspirin, both short- and long-term, was particularly effective at reducing the risk of acute myocardial infarction and/or death (Table 2). Subgroup analysis in the RISC study also showed that the risk of myocardial infarction was reduced both in patients with silent ischaemia as well as in those with asymptomatic ischaemia detected during a presdischarge exercise test. However, doubt remains as to whether aspirin can affect the incidence or severity of myocardial ischaemia after an episode of unstable angina. However, the drug did reduce incidence of death and myocardial infarction in patients with this syndrome, regardless of any influence on episodes of transient ischaemia.

Although the results of most early studies in the benefits of aspirin against secondary cardiovascular events in patients with suspected acute evolving myocardial infarction and acute nonfatal myocardial infarction were consistent with the benefits of antiplatelet therapy, most trials were too small individually in sample size. In 1988, an overview was published by the Antiplatelets Trialists' Collaboration of the 25 completed trials in secondary prevention, followed by an updated overview in 1994. The results are summarised in Table 3 and, together with those of the Second International Study of Infarct Survival, demonstrate the effectiveness of antiplatelet treatment in promoting survival following myocardial infarction. Moreover, in the latter study, the combination of aspirin with intravenous streptokinase proved to be more effective than either agent alone. In absolute terms, the percentage reductions observed imply that the treatment of 1000 patients with acute myocardial infarction with aspirin for one month would prevent 38 fatal and nonfatal cardiovascular events.

The efficacy of aspirin in reducing the risk of recurrent vascular complications in patients with a history of transient ischaemic attacks or stroke was evaluated in various trials. An overview of these trials carried out by the Antiplatelets Trialists' Collaboration concluded that the administration of antiplatelet therapy for three years was effective at reducing the risk of nonfatal stroke, nonfatal myocardial infarction and cardiovascular death by about 25%, respresting, in absolute terms, the prevention of 37 cardiovascular events per 1000 patients over three years. Some doubt remains over the magnitude of the aspirin dose which is effective; while some investigators claim that larger doses are more effective, patients receiving larger doses in those studies reporting a beneficial effect were also receiving other antiplatelet drugs, in particular dipyridamole and sulfinpyrazone.

Maintenance of Vascular Grafts or Arterial Patency

A further outcome of the overview conducted by the Antiplatelets Trialists' Collaboration was the evidence of the benefits provided by antiplatelet therapy in reducing the incidence of arterial or graft occlusion after coronary-artery surgery (30% decrease) or angioplasty (50% decrease), and after the formation of a haemodialysis shunt or fistula (56% decrease). The data provided represented absolute benefits of 90 patients protected per 1000 over 7 months following coronary artery surgery, 40 patients per 1000 over 6 months following angioplasty, and 200 patients per 1000 over two months following formation of a haemodialysis shunt. The same group also concluded that antiplatelet therapy was effective at reducing the incidence of deep vein thrombosis and pulmonary embolism by 26% and 64% respectively, respresenting absolute prevention in 90 and 17 patients, respectively, per 1000 treated. While effective prevention was observed in a wide range of medical and surgical patients, the highest benefits were seen in general and orthopaedic surgery.

Side Effects and Safety of Antiplatelet Therapy with Aspirin

The regulation of several homeostatic mechanisms, including haemostasis, renal function, gastric acid secretion and blood pressure control, is modulated locally through eicosanoid synthesis. Inhibition of the constitutive prostaglandin G/H synthase pathway responsible for the production of these mediators is essentially responsible for the side effects associated with the long term administration of aspirin.

Gastrointestinal complications, such as bleeding and perforation, are observed with greater frequency in individuals on nonsteroidal antiinflammatory therapy. The incidence and severity of these complications are effected by the dosage regimen, the duration of treatment and the type of formulation used (plain vs enteric-coated). Comparison of daily doses of 900 to 1300 mg daily (300 or 325 mg three times daily) as against placebo for various studies exhibited a 40 to 60% increased incidence of stomach pain, heartburn and nausea. On the other hand, both the Veterans Administration Cooperative Study and the Research Group on Instability in Coronary Artery Disease in Southeast Sweden (Table 2) noted only minor increases in the frequency of gastrointestinal symptoms with daily doses of 324 mg and 75 mg aspirin, respectively. Similar dose-dependant results were also obtained by the United Kingdom Transient Ischaemic Attack (UK-TIA) Trial, which noted a 19% increase in upper gastrointestinal symptoms in patients given 300 mg aspirin daily over placebo, and a 58% increase in patients given 1200 mg daily.

The incidence of haemorrhagic

Table 2: Percent reductions in risk of death or acute myocardial infarction in trials among patients following episodes of unstable angina or nonacute myocardial infarction.

Study	Type of Subjects	Aspirin Regimen	Percent reduction
Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC)	796 male patients	75 mg daily for 5 days 75 mg daily for 3 months 75 mg daily for 1 year	57-69% 64% 48%
Veterans Administration Cooperative Study	1,266 male patients	324 mg daily for 3 months	51%
Canadian Multicenter Trial	555 patients	325 mg 4 times daily for 2 years	30%

Table 3: Percent reductions in cardiovascular events among patients with suspected acute evolving myocardial infarction and acute nonfatal myocardial infarction.

Endpoint	Percent reductions in patients assigned antiplatelet therapy	
	Antiplatelet Trialists' Collaboration (long-term therpy; 1-3 years)	2nd International Study of Infarct Survival (short-term therapy; 5 weeks)
Nonfatal myocardial infarction	31	49
Nonfatal stroke	39	46
Cardiovascular mortality	15	23
Cardiovascular events	25	28

stroke amongst patients involved in antiplatelet studies was too small to permit any comparison amongst different aspirin dosage regimens. However, the UK-TIA Trial did observe a dose-response relation for extracranial haemorrhagic events, with an increased incidence of gastrointestinal haemorrhage at higher doses (5% incidence for patients taking 1200 mg aspirin daily, as against 3% for those taking 300 mg daily), possibly reflecting the presence of more severe gastric mucosal damage and thus a higher possibility of gastric bleeding.

Long-term administration of aspirin may also be associated with an increased risk of chronic renal disease and interference with blood pressure control in hypertensive individuals, since prostaglandin G/H synthase is involved in the renal synthesis of vasodilatory prostaglandins. While the use of aspirin at sub-antiinflammatory doses is unlikely to exert any effect (aspirin is only a weak inhibitor of renal prostaglandin synthase), the UK-TIA trial noted elevations in systolic blood pressures in patients on 300 mg and 1200 mg aspirin daily. Furthermore, this effect of aspirin in both renal and other peripheral tissues interferes with the action of angiotensin-converting-enzyme (ACE) inhibitors in controlling hypertension.

Conclusions

The benefits to be derived from long-term aspirin therapy are evident, particularly in secondary prevention of cardiovascular events. The progress in the understanding of the underlying mechanism of action of the drug and its dose-response relationship have led to the current recommendations of an initial loading dose of about 300 mg followed by a daily dose of 75 mg, the latter serving to decrease the possible incidence of side effects.

While the role of prescribing aspirin antiplatelet therapy and monitoring of its cardiovascular effects remain strictly that of the physician, the pharmacist, too, has a contribution to make. There exists the danger of the idea spreading among the general population that "an aspirin (or baby aspirin) tablet a day is good for one's health". Such an idea is, at the very least, questionable in the absence of predisposing health conditions and becomes certainly more so if the possibility of side effects and drug interactions discussed above is prevalent.

Nonetheless, the pharmacist remains in an ideal position to identify candidates in whom initiation of such therapy appears feasible, and should take it upon himself/herself to consult with and make recommendations to the patient's physician, particularly where administration of an aspirin antiplatelet dosage regimen might be effective in the prevention of cardiovascular events. ✶

Bibliography

Antiplatelet Trialists' Collaboration (1994) Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. British Medical Journal, 308: 81-106.

Antiplatelet Trialists' Collaboration (1994) Collaborative overview of randomised trials of antiplatelet therapy - II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. British Medical Journal, 308: 159-168.

Antiplatelet Trialists' Collaboration (1994) Collaborative overview of randomised trials of antiplatelet therapy - III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. British Medical Journal, 308: 235-246.

Cairns, J.A., Gent, M., Singer, J., Finnie, K.J., Froggatt, G.M., Holder, D.A., Jablonsky, G., Kostuk, W.J., Melendez, L.J., Myers, M.G., et al. (1985) Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. The New England Journal of Medicine, 313: 1369-1375.

EDTRS Investigators (1992) Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. Journal of the American Medical Association 268: 1292-1300.

Farrell, B., Godwin, J., Richards, S., and Warlow, C. (1991) The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. Journal of Neurology, Neurosurgery and Psychiatry, 54: 1044-1054.

Hansson, L., Zanchetti, A., Carruthers, S.G., Dahlof, B., Elmfeldt, D., Julius, S., Menard, J., Rahn, K.H., Wedel, H., and Westerling, S. (1998) Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principle results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet, 351: 1755-1762.

Hennekens, C.H. (1997) Aspirin in the treatment and prevention of cardiovascular disease. Annual Review of Public Health, 18: 37-49.

ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. (1988) Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet, 2: 349-360.

Juul-Möller, S., Edvardsson, N., Jahnmatz, B., Rosen, A., Sorensen, S., and Omblus, R. (1992) Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. Lancet, 340: 1421-1425.

Lewis, H.D. Jr, Davis, J.W., Archibald, D.G., Steinke, W.E., Smitherman, T.C., Doherty, J.E., Schnaper, H.W., LeWinter, M.M., Linares, E., Pouget, J.M., Sabharwal, S.C., Chesler, E., and DeMots, H. (1983) Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. The New England Journal of Medicine, 309: 396-403.

Patrono, C. (1994) Aspirin as an antiplatelet drug. The New England Journal of Medicine, 330: 1287-1294.

Peto, R., Gray, R., Collins, R., Wheatley, K., Hennekens, C., Jamrozik, K., Warlow, C., Hafner, B., Thompson, E., Norton, S., et al. (1988) Randomised trial of prophylactic daily aspirin in British male doctors. British Medical Journal, 296: 313-316.

Schrör, K. (1995) Antiplatelet drugs: A comparative review. Drugs, 50: 7-28.

Steering Committee of the Physicians' Health Study Research Group (1989) Final report on the aspirin component of the ongoing Physicians' Health Study. The New England Journal of Medicine, 321: 129-135.

The RISC Group (1990) Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary heart disease. Lancet, 336: 827-830.

Assessment Questions:

Select only ONE option in each question by ticking the respective box on the Response Sheet (page 39).

1. Platelet aggregation is caused by release of:
a) prostaglandin G_2
b) prostaglandin synthase
c) thromboxane A_2
d) acetylsalicylic acid

2. A once daily aspirin antiplatelet regimen is effective because:
a) very high doses of aspirin are used
b) the drug accumulates intracellularly from where it is gradually released
c) sustained release preparations are used
d) recovery from the effects of aspirin is related to platelet turnover

3. Aspirin is effective as a primary preventive agent in:
a) hypertensive patients
b) perfectly healthy individuals
c) patients with chronic stable angina
d) both (a) and (c)

4. The minimum aspirin dose effective in secondary prevention in patients with unstable angina is:
a) 324 mg daily
b) 75 mg daily
c) 1200 mg daily
d) subject to debate

5. The minimum aspirin dose effective in secondary prevention in patients with a history of transient ischaemic attacks is:
a) 324 mg daily
b) 75 mg daily
c) 1200 mg daily
d) subject to debate

6. In order for a beneficial effect to be observed with aspirin therapy in patients with acute MI, therapy must last for at least:
a) about 3 years
b) about 2 years
c) about 1 year
d) slightly more than 1 month

7. Aspirin can prevent arterial or graft occlusion after:
a) coronary artery surgery
b) coronary artery angioplasty
c) formation of a haemodialysis shunt
d) all of the above

8. The highest benefit in reduction of deep vein thrombosis and pulmonary embolism is seen in:
a) all medical and surgical patients
b) all surgical patients
c) general and orthopaedic surgery patients
d) all medical patients

9. The major underlying mechanism responsible for the side effects of aspirin is:
a) direct erosion of the intestinal lining, since aspirin is an acid
b) inhibition of the constitutive prostaglandin synthesis pathway
c) metabolism by the liver to toxic metabolytes
d) none of the above

10. Gastrointestinal complications with aspirin:
a) occur more frequently at higher doses
b) occur less frequently at lower doses
c) exhibit a dose-dependent response
d) all of the above

11. Aspirin-mediated inhibition of prostaglandin synthesis:
a) has no effect on blood pressure control in hypertensive individuals
b) can result in undesirable drug interactions with captopril and enalapril
c) has been observed to result in elevations in diastolic blood pressure
d) probably occurs even at maintenance doses of 75 mg daily.

12. The recommended aspirin dosage regimen for antiplatet therapy is:
a) an Alka-Seltzer tablet daily
b) 300 mg aspirin q.i.d.
c) an initial loading dose of about 300 mg followed by a daily dose of 75 mg
d) none of the above

13. The minimal aspirin dose which will result in practically total suppression of platelet thromboxane A_2 biosynthesis is:
a) 75 mg
b) 100 mg
c) 300 mg
d) 1200 mg

14. The gastrointestinal side effects associated with prolonged use of high dose aspirin include:
a) stomach pain
b) heartburn
c) diarrhoea
d) both (a) and (b)

15. If a patient asks a pharmacist whether it is recommendable to take an aspirin tablet a day for good health, the pharmacist should:
a) answer with an unequivocal yes
b) check if the patient is hypertensive or has a history of cardiovascular events
c) refer to a physician
d) both (b) and (c)

16. Aspirin plays a major role in preventing secondary cardiovascular events in patients with:
a) unstable angina
b) a history of acute myocardial infarction but not nonacute MI
c) a history of any form of MI
d) both (a) and (c)

17. The main indicators in the effectiveness of aspirin in both primary and secondary prevention of occlusive cardiovascular disease are:
a) decrease in mortality
b) decrease in incidence of MI
c) both of the above
d) none of the above

18. How does the combination of aspirin with intravenous streptokinase compare with the use of either agent alone in promoting survival following MI?
a) The combination is more effective
b) The combination is less effective
c) The combination is equally effective
d) There is no clear evidence for a conclusion to be reached.

19. Other drugs which are sometimes combined with aspirin for antiplatelet activity include:
a) dipyridamole
b) enalapril
c) sulfinpyrazone
d) both (a) and (c)

20. The incidence and severity of gastrointestinal complications associated with long-term aspirin use are effected by:
a) dosage regimen
b) duration of treatment
c) the type of formulation used
d) all of the above

Community Pharmacists' Involvement with Substance Abusers, Alcoholics & Their Families

Media liaison committee Sedqa

Introduction

Most people visit the pharmacy to purchase medication. Customers ask for pharmacists for advice on the use of their medication and on the management of their condition, thereby giving them an opportunity to build a professional relationship. Those who have difficulties with substance abuse may be afraid that they will be identified and try to ensure anonymity as much as possible. This may be antagonistic to building a relationship with the person, however, clients tend to obtain their medication from the same pharmacy.

Many drugs abusers are polydrug users and not only use illegal drugs, but also misuse drugs that could be bought over-the-counter with or without a prescription. They could abuse drugs that a relative has been prescribed for mental health conditions. The drug abuser does everything in order to maintain his/her habit. Besides, many alcoholics have prescribed medication and this could be misused with alcohol. Overdoses still occur through the misuse of certain types of medication together with illegal drugs and alcohol.

Knowledge of signs and symptoms of drug addiction

The community pharmacist has to have a sound knowledge of the signs and symptoms shown by persons who use heroin, ecstasy, cocaine and cannabis and also alcohol. Signs and symptoms could include physical, psychological and social. Other evidence includes paraphernalia attached to substance abuse such as syringes, foil, etc. The community pharmacist should be able to differentiate between the signs and symptoms of different illegal drugs and alcohol.

Substance abusers tend to purchase painkillers and other types of medication that could substitute illict drugs. Usually, these could be bought over-the-counter without a prescription. Getting to know the names of the habitual medication asked for would contribute towards the identification of substance abusers. Besides, many are those who ask for medication that is used in the management of mental health, such as antidepressants, benzodiazepines ect. Ethically and legally it is the pharmacist's responsibility to ensure the appropriate use of the medication despensed. Heroin or cocaine users generally go to health centres for a free supply of syringes, but individuals also buy them from the pharmacy. It would be sensible to investigate the use of such equipment when suspicion arises.

Services available in Malta and Gozo

Many professionals who encounter individuals with substance abuse or alcohol problems are not aware of the services available. Though the pharmacist may not have a deep relationship with his regular or occasional customer, he/she needs to be knowledgeable of the offered. It would be helpful to customers if they find literature available in the pharmacy, about drug abuse and its effect, and the services offered by Sedqa, Caritas, Oasi, AA, NA and other organisations to those who are facing alcohol or substance-related difficulties. Consequently, this could stimulate the customer's interest to ask for help. Publications could be left handy so that the general public could easily take copies without attracting attention. Drug abuse and alcohol related difficulties are more pronounced in certain areas than in others. Statistical knowledge as to the concentration of the drug addiction and alcohol related problems in the respective area would keep the pharmacist on the look out.

Confidentiality and Referral

The pharmacist-customer relationship provides an excellent opportunity for the client to iniciate a conversation and express his wories.

Confidentiality encourages the client to open up and ask for further help. This may be difficult in a "shop-like" environment, open to the general public, therefore a priviate area/consultation room in the pharmacy is necessary for such an encounter. Since substance absurers and alcoholics may feel threatened if a pharmacist takes too much interest in their condition, this needs to be done in a non-judgmental and positive manner. Substance abusers often send their relatives to buy medication. Building a good relationship with these relatives could enable a first contact.

Many families suspect that their sons or daughters or their partners abuse drugs, but are not prepared to admit it. This contact enables them to reach out for help.

The pharmacist could also serve as a liaison between the customer and the doctors at Detox Outpatients or the community workers at Dar Gubbio in Sta. Venera. This liaison enables the customer to start receiving help. Thus it is important to note the three main channels of referral: Detox Outpatients, Community Services and for alcohol absuers, Dar Zerniq in Floriana. Many substance abusers or relatives being to receive help when the problem is relatively serious. To facilitate this liaison, it could be possible to offer a first appointment at the pharmacy. People are afraid to be identified and at times, when relatives, substance abusers or alcoholics are still in the denial phase, they could be reluctant to approach services. Drug abuse speciliasits could initiate contact through a first appointment, free of charge, at the pharmacy clinic. This contact would take the place of a home visit in such cases, enabling the customer to have a more attractive choice.

Sedqa has just launched an informative leaflet aimed at those professionals who may need to refer individuals with drug or alcohol related problems. Further basic information regarding substance abuse and the situations surrounding it are available through monthly seminars organised by the Prevention Division. ✶

For further information contact Roberta Cutajar on Tel: 441014

THE chronic✶ill

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The Pharmacist's Response to the Needs of Patients Undergoing Treatment With Psychotropic Medication

Mary Ann Sant Fournier, B.Pharm., M.Phil.

Completion of Assessment Questions following this article entitles members to one credit towards C.E. requirement.

The usage of psychotropic (Table 1) medication is considerable world wide. In Malta, this can be attested to by the numerous studies that have been conducted by the University of Malta Department of Pharmacy (in conjuction with other institutions and individuals).

This could be an indictment to the prescribing trends of psychotropic medication, and, also, to the structures in place with the objective of controlling the usage but which may also be proving to be the barriers to the timely intervention of pharmacists to influence the rational use of these medicines and to deliver effective pharmaceutical care services.

On the other hand, and most significantly, the traditional informality and accessibility of our community pharmacies do not carry the "stigma" of "psychiatric services", although understandably, some patients do find it difficult to discuss their condition where there is lack of privacy.

Community pharmacists are in a unique position to support community-based patients through advice, counselling and monitoring of their medication regimes; together with providing support, and acting as an information resource, to carers and family members, where relevant.

Pharmacists can also act as "gate-keepers" to the national health services, by referring to the family doctor or caring consultant psychiatrist, those patients who are defaulting or are not able to maintain their medication regime. This necessitates an in-depth knowledge of psychotropic medicines and their use, so that pharmacists are able to effectively influence the management of psychiatric medication and attain therapeutic objectives with outcomes that guarantee the improvement of patients' quality of life.

Pharmacists should also be familiar with the main psychiatric disorders.

In parenthesis, however, one must not overlook the fact that pharmacists' knowledge on medicines may be a determinant factor in "differentially diagnosing" drug-induced mental health disorders and suitably advising, counseling and referring patients for review of their medication.

Psychiatric Disorders: Classification And Range

Psychiatric disorders are classified to identify groups of patients who share similar clinical features so that suitable treatment can be planned and the likely outcome predicted. Diagnosis is "syndrome" based, depending on the symptoms and the phenomena observed; this is due to the fact that aetiology and underlying physical and psychological pathology are still only partially understood.

Two major classifications for Psychiatric Disorders are in use:

- The WHO, ICD-10 - International Classification of Diseases 10th Edition, in use in Malta since 1994;
- The DSM-IV - Diagnostic And Statistical Manual (IV) Of Mental Disorders, Fourth Edition, Washington DC, Criteria American Psychiatric Association 1994

A basic classification of mental illnesses, which would suffice within the context of this review (and is not according to the rigid parameters of either the ICD or DSM), subdivides them into two major groups, psychoses and neuroses.

Psychoses are major mental illness which are characterized by severe symptoms, such as disturbance of thinking, e.g., delusions; and of emotions etc., e.g., hallucinations. They are themselves subdivided into organic psychoses, e.g. dementia, and functional psychoses, e.g., schizophrenia and the affective disorders such as depression and mania . Neuroses have symptoms which are much closer to normal experience. Other disorders include those associated with substance addiction.

Table 1 Psychoactive/Psychotropic

- The term psychoactive embraces all those substances which affect the mind, including narcotics and psychotropic drugs.
- "Psychotropic" covers only those which influence mental processes and can lead to dependence.

Source: World Health Organisation. **Report Of The Working Group On The Role Of Schools Of Pharmacy In The Rational Use Of Psychoactive Drugs.** London, 1989

Table 2 Classification Of Psychotropic Drugs By Chemical And Pharmacological Sub-Groups

- tranquillizers-anxiolytics,
- anxiolytics-antipsychotics
- neuroleptics and antipsychotics
- sympathomimetics
- nootropics
- MAOI
- antidepressants
- antiparkinsonian drugs
- anticonvulsants
- hallucinogenic agents
- additional groups

Source:Psychotropics 1997/98

Table 3 Classification Of Psychotropics Viewed As Drugs Acting On The Central Nervous System

- Hypnotics
- Anxiolytics
- Barbiturates

Drugs Used In Psychoses & Related Disorders

- Antipsychotics
- Antipsychotic Depot
- Antimanic Drugs

Antidepressant Drugs

- Tricyclic And Related Antidepressant Drugs
- MAOI
- SSRIs And Related Drugs
- Other Antidepressant Drugs

Source: BNF, September 1997

Table 4 Rational Use

Rational use means that the right drug will be taken by the right patient, in the right dose, and for the right duration of therapy, and that the risks of therapy will be acceptable.

Source: World Health Organisation. **Report Of The Working Group On The Role Of Schools Of Pharmacy In The Rational Use Of Psychoactive Drugs.** London, 1989.

Psychotropic Drugs: An Overview

It is not within the context of this article to address the individual drug classes,(Tables 2 and 3) but reference will be made to the main drugs in use, particularly, in practice settings, and with regard to, for example, clinically significant drug interactions and side effects, together with other factors which may limit their rational use (Table 4).

Classical (Typical) And Atypical Antispychotics

Historically, the use of the classical typical antipsychotics such as the thioxanthenes, e.g., flupenthixol and clopenthixol, the phenothiazines e.g. fluphenazine, and butyrephenones, e.g., haloperidol, in their various forms, has caused concern about their use including the occurrence of side effects such as extrapyramidal symptoms (EPS), tardive dyskinesia, sudden death, neuroleptic malignant syndrome and hormonal disturbance. Other issues, such as non-compliance which may be due to a lack of patients' and carers' understanding of the condition and the importance of medication to treatment and prevention of relapse, together with antipsychotic polypharmacy, excessive use of anticholinergic drugs, excessive doses of the antipsychotics themselves have also raised concerns.

Doses of atypical antipsychotics e.g., clozapine, have also been reported to be too high. These drugs have been introduced into clinical use relatively recently and have less EPS and prolactin-related effects, but, they do not do not belong to a specific class (hence, atypical).

Clozapine has been reported to be the only atypical antipsychotic with proven efficacy in refractory schizophrenia; while it lacks EPS, it has been associated with a range of other adverse effects including agranulocytosis, necessitating regular blood monitoring in patients requiring this treatment.

Mood Stablilisers

Many mood stablisers are the result of serendipitous discovery. Those in current use include lithium, carbamezapine, sodium valproate and other anticonvulsants, thyroid hormones and calcium channel blockers.

The most common failure of therapy is non-compliance. Mood disorders could be resistant to single agents, polypharmcy is therefore common and pharmacists' focus should be on side effects and interactions.

Lithium with its long half life and narrow therapeutic index requires serum level monitoring. Monitoring is a clear indication of the degree of compliance by patients to the medication and is a valuable tool to educate the patients and inform them on the outcome options basing on their understanding of the importance of their adherence to their treatment plan. Serum levels are also a quality assurance tool of the prescribing practices of lithium, to ensure that patients are not receiving too high or too low a dose, but the right dose for the management of a particular patient.

The pharmacist should focus on the propensity for interaction of lithium with other drugs. The likelihood of the occurrence of clinically significant interactions is increased with drugs that

- induce or inhibit hepatic microsomal enzymes
- have a low therapeutic index
- have a muliplicity of pharmacologic action
- and in high risk patient groups, such as the elderly, mentally ill and substance abusers.

The most common interactions, with a potential tolead to intoxication, are those with Non-Steroidal Anti-inflammatory Drugs, with reported increases in serum lithium levels of up to 60%; and with different diuretics and antihypertensive agents. The concomitant administration of lithium with other psychotropics, such as carbamezapine and other TCAs is relatively safe with strict monitoring of serum lithium levels.

It is suitable to remember that the ingestion of sodium chloride and sodium bicarbonate can cause a decrease in serum lithium levels.

The side-effect profile of lithium must also be given attention. These range from the transient, such as nausea, to the persistent but harmless (and which appear with normal serum lithium levels), such as weight gain, to the ones that are prodromal to intoxication. Pharmacists can help patients to be alert to recognise these symptoms.

Antidepressants

Optimal outcomes can be achieved if commencement of treatment with antidepressants is not delayed, is vigorous and continued for at least 4- 6 months after the initial response. Achievement of these objectives however appear to be limited in practice. resulting in poor patient outcomes in the management of depression.

Pharmacoepidemiological studies suggest that patients who are treated with the older tricyclic antidepressants (TCAs) rarely completed an effective course of treatment, either in terms of receiving an adequate dose of antidepressant or completing a minimum period of treatment when an adequate dose was achieved. Initial choice of antidepressant appeared to be an important factor in determining subsequent treatment patterns; patients who began treatment with a selective serotonin reuptake inhibitor (SSRI) were considerably more likely to complete an effective course of treatment which should be reflected in better outcomes including better quality of life outcomes.

The pharmacist must also be aware of the varied indications associated with the use of the TCAs ,which may preclude their prescription for "psychiatric" needs, but, for example, may be used for the treatment of pain. In giving advice, the pharmacist must identify the prescriber's objective and not volunteer information that might undermine the patient's trust in the prescriber and in the treatment .

Consideration of the pharmacokinetic profile of SSRIs may prove useful to support the choice of medication in specific cases. This is often overlooked and can lead to inadequate treatment and outcome.

Prevention Of Relapse

It is well established that antidepressants, antipsychotics and mood stablisers prevent relapse if taken long-term. This however places a great deal of responsibility on the patients themselves, who will only comply if they accepted that something was wrong, that it needed correcting, that medication would help and that the risk-benefit ratio was acceptable.

Common reasons for discontinuation of psychotropics by patients include side effects (even if manageable), fear of addiction, lack of knowledge that the treatment prevented relapse, and pressure from (usually uninformed)

Table 5 Committee On Safety Of Medicines (UK) Advice

1. Benzodiazepines are indicated for the short-term (two to four weeks only) relief of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
2. The use of benzodiazepines to treat short-term, 'mild' anxiety is inappropriate and unsuitable.
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling or when it is subjecting the individual to extreme distress.

Source: British National Formulary, Number 34 (September 1997)

relatives and friends.

A positive attitude towards their treatment was generally essential for attaining objectives of better outcomes, particularly in the long term. A number of studies have shown the advantages of structured education and support of patients, and the subsequent positive effect on attitude and hence, adherence to treatment plans, prevention of relapse and quality of life.

Hypnotics and Anxiolytics

Benzodiazepines (Table 5) are the most commonly used anxiolytics and hypnotics. Studies have shown that in 1989, 11.92% of the Maltese population had consumed benzodiazepines; and since 1993, there has been a change in the prescribing trend towards the shorter acting benzodiazepines such as lorazepam and triazolam, especially in the elderly (<66yrs).

However, in 1995, there were still a high 48.4% of elderly patients receiving long acting benzodiazepines such as, diazepam, Subsequently, it was confirmed that, in 1997, there was a consistent increase in benzodiazepine prescribing in the 45-65 age group. Females are also consistently reported to be the largest group of patients consuming benzodiazepines, accounting for more than double their male counterparts.

The needs of all patients to whom benzodiazepines have been prescribed should be addressed by pharmacists who should refrain from acting as "passive conduits" complying to the legal requirements alone in the dispensing of benzodiazepines. Some of these needs are of a general nature whilst others are specific to the age group and, in some cases, to the gender concerned e.g. pregnancy and lactation.

It is to be emphasized that benzodiazepines have a "broad spectrum" of indications and may also be prescribed for their action as e.g., muscle relaxant, anticonvulsant and antiepileptic properties.

Dosage and dosage regimens require particular attention not only from the legal supply aspect but with consideration to the management of the condition, prevention of misuse and the possible diversion of benzodiazepines to illicit use.

In consideration of adverse effects of benzodiazepines, the potential for the development of tolerance, dependence (Table 6) and the withdrawal syndrome must be given due regard. For example, patients should be warned of the effect of abrupt discontinuation of the medication which can result in increased anxiety, sleep disorder, aching limbs, nervousness, nausea, and influenza-like symptoms; and referred to their caring physician should they feel ready to discontinue their therapy.

Particularly in the elderly, problems associated with ataxia and consequent falls and injury, confusion, memory loss and cognitive impairment require attention.

The additive effects of benzodiazepines when administered in combination with alcohol and other CNS depressants such as neuroleptics and antipsychotics, hypnotics, anxiolytics and sedatives, antidepressants, narcotic analgesics - which can also lead to euphoria, enhancing the potential for psychic dependence of the latter - antiepileptic drugs and anaesthetics should also be of concern. Other potentially clinically significant drug interactions include the temporary increase of the sedative effect of benzodiazepines by the concomitant administration of cispiride; the possible enhancement of the activity of benzodiazepines by those drugs which inhibit certain hepatic enzymes particularly cytochrome P 450.

Zolpidem and chlormethiazole have a place as hypnotics for short term use,

Table 6 Definition - (Substance) Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the following ocurring at any time in a time period:

1) tolerance, as defined by either of the following:
   a) need for markedly increased amounts to achieve (intoxication or) the desired effects
   b) markedly diminished effect with continual use of the same amount,
2) withdrawal, as manifested by either of the following:
   a) the characteristic withdrawal syndrome for the substance
   b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
3) the substance is often taken in larger amounts or over a longer period than was intended
4) there is a persistent desire or unsuccessful efforts to cut down or control substance abuse
5) a great deal of time is spent in activities necessary to obtain the substance e.g. visiting multiple doctors or driving long distances, use the substance (e.g. chain-smoking) or recover from its effects.
6) important social occupational, or recreational activities are given up or reduced because of substance abuse;
7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem is caused or exacerbated by the substance.(e.g. continuing to drink alcohol despite ulcer in stomach)

Source: Adapted from Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington DC, Criteria American Psychiatric Association 1994

the latter particularly in the elderly. Their relative freedom from a 'hang-over' effect makes them particularly useful drugs. Chlomethiazole has a place in the treatment of alcohol withdrawal in the younger patients. Pharmacists should be vigilant for the phenomenon of abuse that has recently been associated with the use of these drugs.

Psychotropic Medication and Driving Performance

Benzodiazepines together with other psychotropic drugs such as sedating tricyclic antidepressants, many anticonvulsants, neuroleptics may adversely effect driving performance and also the operating of machinery. Patients should be warned that drowsiness and impairment of psychomotor function as produced by sedating TCAs can impair driving performance.

This can occur with some drugs only on the first few days of treatment, but subsequently, there can be a slowing of reaction time and loss of mental concentration Moreover, psychotropic drugs can alter the patients' perception of their driving skills and the dangers on the road.

Drug induced side effects unrelated to drowsiness can also impair patients ability to drive. These include anticholinergic side effects also associated with the TCAs ,such as blurred vision, dizziness and nausea. Patients should be advised for example, not to drive if unwell, to stop immediately, and take small breaks.

Long acting hypnotics and anxiolytics are associated with daytime sedation and drowsiness, together with impaired performance of complex hand-eye coordination tasks, increased reaction time and impaired cognitive function.

Attention should also be given to the potential interaction of dispensed pharmacist recommended medicines with these prescription drugs.

Needless to say, the combination of alcohol with these medicines exacerbates these effects, especially in the elderly.

Pharmacists should clearly warn patients, both verbally and in writing, of these serious potential effects on traffic safety. A written note will act as a reminder when they are home.

Table 7 Case Study - An Example of Pharmaceutical Care Considerations Of Patients Undergoing Treatment With Psychotropic Medication

Mrs. Borg is a 55 year-old woman who presents her pharmacist with a prescription for a maintenance dose of a combination product containing fluphenazine hydrochloride 500 mcgs and nortriptyline 10 mgs. Mrs. Borg says that she is undecided whether to continue with her treatment since she has noted that she has been putting on weight and this is further increasing her distress.

- The pharmacist notes that Mrs. Borg is not a new patient, but on referring to the daily register, he notes that a number of months have elapsed since she has come to the pharmacy to refill her prescription.
- The pharmacist is concerned that if Mrs. Borg defaults on her therapy she could suffer a relapse. This would be a great pity as Mrs. Borg has been successfully controlled and maintained in the community where she has been improving her quality of life.
- The pharmacist takes the advantage of not having any patients or other clients in the pharmacy at the time and asks Mrs. Borg to sit down in a quiet corner and tell him more about her concerns.
- As she sits down, Mrs. Borg says that since her only son's wedding 3 months ago, she has found that she has plenty of time to herself and has taken to sit for long hours watching television and eating her favourite chocolates. She has also found that she has more time to sit at table with her husband during meals and has been adding little gourmet pleasures to their normal menu.
- The pharmacist explains that whilst the medicine itself may be responsible for some weight gain, the changed eating habits may have been more decisive in her case. Since the depression had been well controlled and she was feeling better, the pharmacist reinforced his counselling to empower Mrs. Borg to understand her condition and to achieve concordance with the medication regimen, with advice on healthy eating habits and other lifestyle modifications, including, exercise such as walking and the taking up of a hobby. He also gave her a leaflet in Maltese called "Kul ghall-sahtek" together with another one on depression.
- Mrs. Borg agreed to take the medicine for a month, after which she would return to the pharmacy to weigh herself. The pharmacist then invited her to check her weight and recorded it. He suggested that should there be no decrease in her weight after one month, then he would refer her to her family doctor for review of her medication.

Conclusion

Pharmacists are in an ideal position to respond to special needs of psychiatric patients (Table 7) .They can:

- identify undiagnosed conditions, eg, depression, and refer to family doctor;
- reassure patients and carers and encourage them to seek treatment;
- support vulnerable patients and involve carers and/or family, whilst ensuring confidentiality;
- educate patients about their condition and its management and in particular, about their medication;
- encourage compliance and concordance, without ignoring patient vulnerability;
- monitor patient progress and avoid or minise adverse drug effects to achieve therapeutic objectives and improve patients' quality of life;.
- liase with other health professionals for better patient care and outcomes.

Through a concerted endeavour the barriers preventing pharmacists' full interventions in this important area of care can be identified and overcome. This is most significant at this moment in time when the health system is moving towards a policy of decreasing institutionalisation of psychiatric patients and enhancing community based services, Pharmacists are the natural but still underutilised resource for this highly vulnerable patient group, their families and carers and the health system. ✶

Bibliography

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, Criteria Fourth Edition, Washington DC

Association of European Psychiatrists. (1998) Optimising Drug Therapy In Various Psychiatric Conditions. Pharmaceutical Journal , 26: 831.

British Medical Association and Royal Pharmaceutical Society of Great Britain (1997) British National Formulary Number 34, London and Oxon.: 154.

De Prins, L., (Ed) (1997) Psychotropics 1997/1998. H. Lundbeck A/S., Denmark.

Debono, H. (1992) Schizophrenia in Malta. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

Fenech, K. (1996) The Prescribing and Use of Benzodiazepines in Malta. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

Magro, G. (1996) The Rational Use Of Clozapine In Schizophrenia. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

Muscat, P., (Ed) (1996) Handbook of Psychiatry. Revised edition. Department of Psychiatry, University of Malta, Malta.

Pace, E. (1998) Benzodiazepines Current Trends And Usage In Malta. In Pharmacy Symposium Project Reports, Seracino Inglott, A. (Ed) Department of Pharmcy University of Malta, Malta. 167-171.

Preca, F. (1991) Trends in Benzodiazepine Use In Malta. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

Ross, Ingrid (1994) Compliance to Lithium Therapy in Affective Disorders in Malta. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

Royal Pharmaceutical Society Of Great Britain (1989) Council Statement, London. Royal Pharmaceutical Society Of Great Britain, London.

Sant Fournier, M.A. (1991) Psychotropic Medication in the Elderly. In: Drugs In The Elderly, Proceedings of the International Symposium. Department of Pharmacy, University of Malta, Secretariat for the Care of the Elderly, University Press, Malta, Rizzo Naudi, J. and Serracino Inglott, A. (Eds). University Press, Malta: 93-112.

Shaw, C. (1998) A Drug Utilisation Review at a Psychiatric Hospital. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

Tabone, M. (1994) Alcohol, Drugs and Driving Performance. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

World Health Organisation (1989) Report Of The Working Group On The Role Of Schools Of Pharmacy In The Rational Use Of Psychoactive Drugs. WHO, London.

World Health Organisation (1993). The ICD - 10 Classification of Mental and Disorders-Diagnostic Criteria For Research, WHO, Geneva.

Zammit S. (1998) Rationalising the Use of Selective Serotonin Reuptake Inhibitors. Pharmacy undergraduate project, Department of Pharmacy, University of Malta, Malta. (unpublished).

"Pharmaceutical care requires co-operation, communication and consistency among pharmacists as well as between pharmacists and other professionals."
Hepler

The Pharmacist's Response to the Needs of Patients Undergoing Treatment With Psychotropic Medication

Assessment Questions:

Select only ONE option in each question by ticking the respective box on the Response Sheet (page 39).

1. Community Pharmacies can offer professional care services to psychiatric patients because pharmacies are:
   a. not identified with" psychiatric services"
   b. can offer privacy facilities
   c. assure confidentiality
   d. all of the above
2. Pharmacists can support community based psychiatric patients by:
   a. offering advice and counseling on their treatment
   b. monitoring progress and outcomes
   c. providing support to patients and carers
   d. all of the above
3. To influence the rational use of psychotropic medicines pharmacists must
   a. be familiar with the main psychiatric disorders
   b. be familiar with drug induced mental health disorders
   c. have insight into the needs of psychiatric patients
   d. all of the above
4. A side effect which is specific to the use of clozapine is
   a. tardive dyskinesia
   b neuroleptic malignant syndrome
   c agranulocytosis
   d prolactin-related
5. The likelihood of occurrence of clinically significant interactions of lithium is increased
   a. with drugs that have a low therapeutic index
   b. with drugs that have a multiplicity of pharmacological action
   c. in high risk patient groups
   d. in all of the above situations
6. The concomitant administration of lithium with one of the following drugs is relatively safe with strict serum lithium levels monitoring
   a. NSAIDs
   b. anthypertensives
   c. diuretics
   d. carbamezapine
7. Optimal outcomes in depression can be achieved if treatment is
   a. is discontinued on achieving response
   b. is delayed
   c. is continued for at least 4-6 months after initial response
   d. none of the above.
8. Patients who are treated with the older TCAs
   a. rarely complete an effective course of treatment
   b. may not receive an adequate dose of antidepressant
   c. may not complete a minimum period of treatment when an adequate dose was achieved
   d. may not be suffering from psychiatric illness
   e. all of the above
9. Patients who are treated with an SSRI
   a. have poorer outcomes than with TCAs
   b. are more likely to complete an effective course of treatmeny
   c. do not have better quality of life outcomes than with older TCAs.
   d. all of the above
10. Antidepressants, mood stabilisers and antipsychotics prevent relapse if taken long-term, depending on whether
    a. patients accept that something is wrong with them
    b. patients accept that what is wrong with them needs correcting
    c. patients accept that medication would help
    d. all of the above
11. Common reasons for the discontinuation of psychotropic medicines by patients include
    a. side effects (even if manageable)
    b. fear of addiction
    c. lack of knowledge that treatment prevented relapse
    d. all of the above
12. Prolonged treatment with benzodiazepines can result in
    a.influenza-like symptoms
    b.withdrawal syndrome
    c. .tolerance and dependence
    d. all of the above
13. The abrupt discontinuation of benzodiazepine treatment can result in
    a. anxiety
    b. influenza-like symptoms
    c. sleep disorder
    d. all of the above
14. Which of the following should be registered in the Register of Psychotropic drugs
    a. citalopram
    b. zolpidem
    c. chlormethiazole
    d. all of the above
15. Elderly patients on benzodiazepine treatment must receive the pharmacist's special attention with regard to
    a. possibility of falls and injury
    b. confusion
    c. memory loss and cognative impairment
    d. all of the above
16. Additive effects of concern are a result of the co-administration of benzodiazepines with the following drugs
    a. alcohol
    b. narcotic analgesics
    c. anaesthetics
    d. all of the above
17. The following psychotropic medicines can have serious effects on driving performance
    a. benzodiazepines
    b. neuroleptics
    c. sedating TCAs
    d. all of the above
18. Pharmacists should warn patients on the adverse effects of psychotropic medication on driving performance including
    a. daytime sedation and drowsiness produced by long-acting hypnotics and anxiolytics
    b .daytime induced anticholinergic side effects of TCAs such as blurred vision, dizziness and nausea
    c. impaired performance of complex hand-eye coordination tasks, increased reaction time and impaired cognitive function produced by benzodiazepines
    d. all of the above
19. Pharmacists can respond to the needs of psychiatric patients by
    a. identifying undiagnosed conditions and referring to the family doctor
    b. supporting them and involving carers/family, whilst ensuring confidentiality
    c. monitoring their progress and intervening where necessary in liaison with other carers to achieve therapeutic and quality of life outcomes
    d. all of the above
20. The barriers which preclude pharmacists from being fully effective in delivering pharmaceutical care services to psychiatric patients include
    a. centralised system of the 'free' distribution of several classes of psychotropic medicines to a majority of patients which bypasses the community pharmacists
    b. legislative structures controlling supply of drugs of dependence which restrict pharmacists' intervention.
    c. pharmacy logistics, such as lack of private area, lack of time, limited computerisation and lack of teamwork with other health professionals
    d. all of the above

Booklets have been produced by the Department of Pharmacy, University of Malta as part of BPharm(Hons) projects.

These include:

- It-terapija tal-Lithium - X'ghandu jkun jaf il-pazjent. There is also an accompanying video on this subject in English and Maltese
- The Pharmacist and Safe Driving - The Influence Of Medicines, Alcohol And Drugs on Driving

Other printed material includes:

- Is-sahha mentali - Department of Health Promotion

Sedqa leaflets

- Stop Droga campaign booklets and leaflets, Malta Chamber of Pharmacists

Pharmaceutical Companies with an interest in Psychiatry also produce patient-oriented leaflets on mental disorders, their treatment and management.

Response Sheet

Page 5
Management of Migraine
Isabelle Farrugia

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Page 13
The Treatment of Asthma with Leukotriene Receptor Antagonists
Maria Cordina

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Page 21
The Antiplatelet Activity of Aspirin
Claude A. Farrugia

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Page 31
The Pharacist's Response to the Needs of Patients Undergoing Treatment with Psychotropic Medication
Mary Anne Sant Fournier

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For Official Use

Correct Answers

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Article 2 ☐
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