Pharmaco Logical

The Newsletter of the Rational Use of Medicines Directorate
Ministry of Health, Sultanate of Oman

Volume 4 Number 1, March 2008

Welcome to the fourth year and seventh issue of the newsletter.

The new name of the directorate of rational use of medicines (DRUM) has quickly gained acceptance by almost everyone and is appearing more and more in communications as well as on the fascia of the office.

This will be a busy year with many new schemes coming in to affect us all such as the continuing professional development accreditation scheme. Our directorate will have many workshops in 2008 focussing on update of research skills and statistics, intervention and project design, use of defined daily doses (DDD) and anatomical, therapeutic and chemical (ATC) codes. There will be increasing emphasis on clinical pharmacy and solving various pharmaceutical care issues.

Contributors to this issue

Ph Batool Jaffer Suleiman	*Director, DRUM*
Ph Manal Al-Ansari	*Pharmacist, DRUM*
Dr Ahmed Abdo-Rabbo	*Pharmacologist, DRUM*
Dr Hawraa Al-Lawati	*Physician, DRUM*
Dr Brian Gunn	*Clinical Pharmacist, DRUM*

Edited by Dr Brian Gunn

New Staff Member

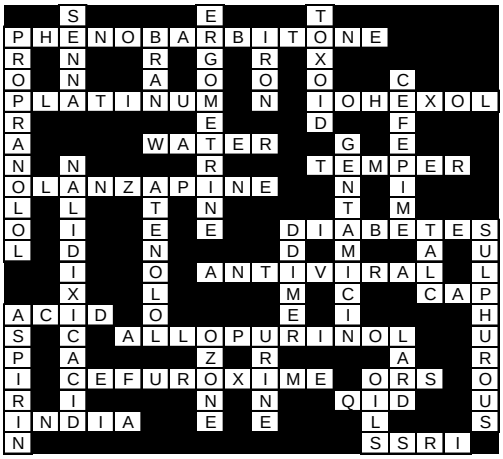
It is a pleasure to introduce to you a new member of staff at DRUM, Dr Hawraa Al-Lawati.

Dr Hawraa has joined the directorate from Primary Health Care. Her skills as a physician will be very useful to the directorate in many different clinical areas.

Crossword Competition

Solution to the crossword puzzle in the last edition (*Volume 3 Number 2, September 2007*).

Note that the drug names in the grid are strategically arranged to direct you to the correct spelling!



Congratulations to **Pharmacist, C L Safarullah** of Jaalan Bani Bu Hassan Hospital, South Sharqiyah Region who submitted the only all correct answer.

Commiserations to runner-up Assistant Pharmacist, **Irfan Ahmed Khan** of Shinas EHC, North Batinah Region, who had one small error (CUP instead of CAP).

As per the above you will note that in the last issue (*Volume 3, Number 2 September 2007*) there was a prize crossword and in this issue there is a word search puzzle on the back page. These puzzles can be, and are often, used for educational purposes.

In the two puzzles that have been used in these editions of the newsletter the focus is really about the proper spelling of drug names!

Too often, even in official documents and publications drug names are carelessly spelt and this is embarrassing as well as potentially dangerous. Drug names need to be spelt correctly and especially when hand written. The internet has many sites devoted to medicinal drugs but many are substandard and contain incorrect information and advice. It is often easy to distinguish a good site from a poor site by how the drug names are spelt.

If you ever find the drug name written like "**gentamycin**" for example it is unlikely that you can totally trust the information contained in the web - site.

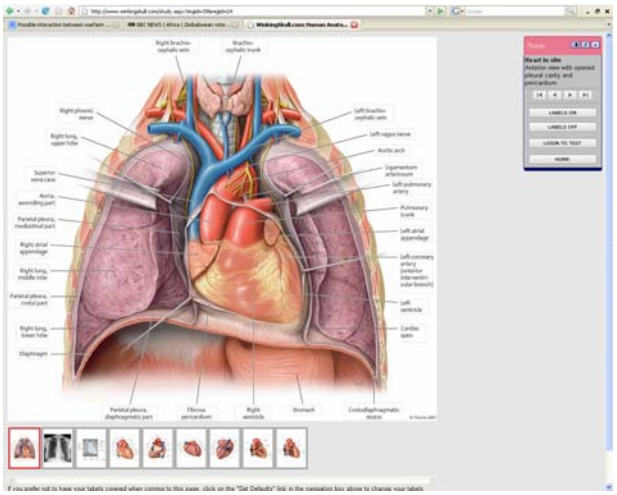
As English is not the mother tongue here in Oman it is understood that English spellings in general, 'p', 'b' and 'g' and vowels in particular are often very difficult, but we should all make the effort to get the names right in our writings all the time!

Everyone who uses a word processor should make sure they add the correctly spelt drug name to their custom dictionary that pops up during a spell check. By this means the spelling should always be correct but again, *be careful*, as the custom dictionary will accept anything you put into it.

Try This Site

http://www.winkingskull.com/navigation.aspx

One of the best anatomy sites on the web.



You have to register to get most of the benefits and do tests but registration is free. You can have the key elements labelled or not or you can uncover any individual label to determine the name of a structure. The thumbnail strip across the bottom shows which views are available. It is excellent for revision or for learning.

Placebos

Dr Hawraa Al-Lawati

A placebo (Latin for *"I shall please"*) can be defined as any inactive substance, such as a sugar pill, used to replace medication. In clinical trials, placebos are given to blind control groups used in clinical research to compare the results with those of an experimental drug. The experimental treatment must produce better results than the placebo in order to be considered effective.

From the former definition, the placebo effect can be viewed in two different ways:

- The effect of a placebo in medical practice.
- The effect of a placebo in clinical trials.

Placebos in medical practice:

Many believe that the effect of a placebo is mainly psychological and related to a patient's expectations of cure. If a patient thinks that the pill will help, it will help and vice versa.

However, there is no evidence that placebo treatments in general have important effects, although they may have small effects on patient-reported outcomes, for example pain.

It has been widely believed that placebo (dummy) treatments are associated with substantial effects on a wide range of health problems. However, this belief is not based on evidence from randomised trials that use a placebo treatment for one group of people, while another group receives no treatment. The effect of placebo treatments was studied by reviewing more than 150 such trials covering many types of health care problems. Placebo treatments caused no major health benefits, although they possibly had a small effect on outcomes reported by patients, for example pain. (The Cochrane Collaboration)

In addition, the magic effect of placebo might not be related to placebo itself but rather to the variability of the natural course of the disease. This is very obvious in chronic diseases where there are usually ups and downs e.g. arthritis, SLE….etc.

Although placebo use is not legally approved by many health systems in the world, some physicians do prescribe true medicines which contains active ingredients to get an effect similar to that of placebo. E.g.: saline injections given for pain that is thought to be fictitious, or to prescribe unnecessary antibiotics or under-dose of a drug to satisfy the patient, end the consultation early or to accelerate the treatment. This can act as a distraction, delay the diagnosis and alter the therapeutic relationships.

Nobody can ignore the psychological impact in the contribution / aggravation of any disease but instead of using placebo, it is possible to reinforce the patient's expectations to get well by other reasonable, effective and long lasting means like building good doctor-patient relationships, increasing patients' awareness and psycho-social therapy.

Placebos in clinical trials:

The history of the placebo-controlled trial

The first known double-blind placebo-controlled trial was performed by W.H.R. Rivers in 1907 to investigate the influence of alcohol and other drugs on fatigue (1). A few placebo-controlled studies appeared during the 1920s and 1930s, but most of these were not blinded. Much of the credit for establishing double-blind placebo-controlled design as the gold standard for clinical trials goes to a pharmacologist named Harry Gold (1). In addition to conducting a number of trials, Gold lectured and published extensively on the double-blind placebo-controlled design in the 1940s and 1950s. In the 1970s, the FDA started recommending and now requires that safety and efficacy studies of new drugs use a double-blind design with placebo controls whenever ethical and feasible (1).

The knowledge about the placebo effect was very much enlarged with the medical need to perform controlled clinical trials, a scientific methodology largely used to determine the therapeutic effectiveness of new medicines.

Even with the powerful scientific advantages of including a placebo in the medical researches, it is important that the use of placebo is appropriate, safe and ethical.

E.g.: in oncology, placebo-controlled studies are often unacceptable because of the great risk to cancer patients of any treatment delays.

In such situations, it is crucial to know that the FDA does not require that a drug study include a placebo control group. Non-placebo types of drug studies include "head-to-head" studies, which compare the experimental drug to an existing treatment, and historically controlled studies, which compare the new drug's effects with information gathered in the past about the expected progression of a medical condition.

References:

1. Shapiro, A. K.; Shapiro, E. The Powerful Placebo: From Ancient Priest to Modern Physician. Johns Hopkins University Press: Baltimore, MD, 1997; p 272.

Also see:
http://www.cochrane.org/reviews/en/ab003974.html
http://www.fda.gov/fdac/features/2000/100_heal.html
http://www.thefreedictionary.com/placebo

DRUM Roll

Recent Events:
DRUM has recently been involved in several workshops:

Al Nahdha, Hospital PG Centre, Presentation on Medical Errors

Adh Dakhliyah Region, in collaboration with OmPhS, Workshop on Drug Utilisation Research for Pharmacists and Assistant Pharmacist

South Batinah Region, Workshop on Rational Prescribing and Use of Medicines. For Physicians and Pharmacists in North and South Batinah Regions

Be Aware

Ph Batool Jaffer Suleiman

Many people do not realise that certain food additives can increase hyperactivity in susceptible children. Attention deficit disorder (ADD) and attention deficit hyperactivity disorder or ADHD are recently recognised but still controversial chronic conditions appearing mainly in children but which can continue into adult life. A study carried out by the University of Southampton, UK found that 28 medicines out of 70 studied contained one or more suspect additives. Sixteen of the products were designed for use by very young children (under 3 years).

Surveyed medicines for all children included:

Product	Number of products in survey	Number using one or more of the seven suspect additives
Paracetamol	37	17
Ibuprofen	11	2
Amoxicillin	5	3
Erythromycin	8	2
Throat Linctus	9	4
Total	70	28

Many of the non antibiotic medicines are available as over-the-counter products and are available in pharmacies and some supermarkets.

The seven suspect additives are shown in the following table:

E – Number	Additive
E102	Tartrazine
E104	Quinoline Yellow
E110	Sunset Yellow
E122	Carmoisine
E124	Ponceau 4R
E129	Allura Red
E211	Sodium Benzoate

The first 6 are used as colours and the seventh one is used as a preservative.

As well as hyperactivity many of these preservatives have been linked to certain hypersensitivity reactions such as asthma, rashes and urticaria.

The E numbers are codes used by the European Union and other countries including the GCC[1] to identify several different food and medicine additives. They are usually found on the labels of the package containing the foodstuff. The term “E-number” is commonly used by lay people to mean a bad or harmful additive in foodstuff. Tartrazine or E102 is probably the best known additive and has been suspected as problematic for a number of years. Some foodstuffs claim to be free of “E-numbers” in their advertising even although they will inevitably contain some forms of additive. For a complete listing of all E-numbers please refer to Wikipedia[2] or similar resources.

[1] Gulf Cooperation Council

[2] http://en.wikipedia.org/wiki/E_number

Drug Interactions - Part III

Dr Brian C Gunn

A useful aid to learning and understanding drug-drug interactions is to form a grid or pivot table such as the example below. The list should be made up with the drugs you are interested in and then constructed as shown. If two drugs interact then mark the intersection with e.g. **A** = absorption, **T** = target (organ or process), **M** = metabolism and **E** elimination or excretion. This depends on the main mechanism of interaction.

	Warfarin	Tetracycline	Terfenadine	Propranolol	Phenytoin	Nifedipine	Iron	Fluconazole	Erythromycin	Digoxin	Cimetidine
Aspirin	**T**										**A**
Cimetidine	**M**				**M**	**M**	**A**	**M**	**M**		
Digoxin		**A**			**M**				**E**		
Erythromycin	**M**		**M**		**M**						
Fluconazole	**M**		**M**		**M**	**M**					
Iron		**A**									
Nifedipine				**T**							
Phenytoin	**M**	**M**									
Propranolol			**M**								
Terfenadine											
Tetracycline											

Note that some drug-interactions are not necessarily therapeutically significant**.**

This issue will focus mainly on drug metabolism as this is possibly the most important of the pharmacokinetic interactions.

Metabolism

Phase I reactions – chemical transformations which usually inactivate but can sometimes activate a drug. The main reactions are

oxidation, reduction, dealkylation, hydrolysis

Phase 2 reactions – conjugation (increases solubility of substrate). The main ones are glucuronidation, sulfation, glutathionation, methylation, acylation (in order of importance).

Phase 1 reactions are carried out predominantly by the iso-enzymes of the cytochrome P_{450} family – the microsomal enzymes. The levels of these enzymes are influenced by the genetic disposition. The science of **pharmacogenomics (**or **pharmacogenetics)** is devoted to the study of genetic makeup and how it influences an individual's response to drugs

Drug interactions by induction and inhibition of the isoenzymes. It has been understood for some time that many drugs can interfere with the microsomal enzymes
Some examples are shown in the following table:

P_{450} isoenzymes	Substrates	Inhibitors	Inducers
Cyp1A2	Warfarin	Cimetidine	Phenytoin
Cyp2B6	Bupropion	Thiotepa	Rifampicin
Cyp2C9	Phenytoin	Isoniazid	Rifampicin
Cyp2C19	Diazepam	Ketoconazole	N/A
Cyp2D6	Metoprolol	Cimetidine	N/A
Cyp2E1	Ethanol	Disulfiram	INH
Cyp3A4,5,7	Terfenadine	Erythromycin	Phenytoin

Notice that a drug can have different roles depending on its concentration in the tissues.

Important and common non-drug interactants are grapefruit juice which is an inhibitor of cyp 3A and thus can affect the activity of many common drugs. Cranberry juice which also contains flavanoids is known to prolong the action of warfarin. Also, cigarette smoke is a potent inducer of cyp 1A2.

Getting to know the most common inhibitors and inducers is an excellent first step in understanding and predicting many drug-drug interactions. There are many mnemonics that have been thought up to aid memory retention of many of the more important ones.

Inhibitors	
Ciprofloxacin Cimetidine Fluconazole Isoniazid Ritonavir	**"cip, cim, flu, INH, and rit"**
Inducers	
Carbamazepine Phenobarbital Phenytoin Rifampicin	**"carb, barb, pheny, and rif"**

Clinically significant drug interactions occur predominantly with highly potent and narrow therapeutic index drugs.

Getting to know the most common interactions and the mechanisms involved can rapidly expand your knowledge of many more interactions.

The VEN Categorisation System for Medicines

Dr Brian Gunn

VEN system.

The VEN system is defined as a system of prioritising the purchase, supply and stock holding of medicines on an essential medicines list according to their impact on health. The medicines are categorized as **V**ital, **E**ssential or **N**on-essential[3].

Vital Medicines

These are potentially life saving medicines which may have significant withdrawal effects (making regular supply mandatory) or are fundamental to providing basic health services.
e.g. adrenalin/epinephrine injection, naloxone injection, quinine injection and other antimalarials

Essential Medicines

These medicines are effective against less severe but, nevertheless, significant forms of illness but are not absolutely vital to providing basic health services.
e.g. statins or antihypertensives

Nonessential Medicines

These drugs are normally used for self limiting illnesses or are of doubtful efficacy or have a high cost for a marginal therapeutic advantage. They are a low priority for procurement.
e.g. cough and cold remedies, decongestants.

[3] It seems paradoxical to have a drug on an essential drug list and yet categorized as "non-essential". This confusing terminology has led to **N** being sometimes defined as **N**ecessary or **N**eeded. In some texts you will come across a VED classification and in this case the **D** is defined as **D**esirable.

They should only be purchased in limited quantities if funds are available after other priorities have been assigned.

The Process of Classification

Classification should be done by a representative group of specialists in various fields across an institution e.g. hospital or even a country. Certain medicines can be very difficult to categorise without specialist input. In some cases one specialist's "vital" is another specialist's "essential" or even "nonessential".

Classification is not a one time exercise. It should be a dynamic process and medicines should be reviewed and reclassified if appropriate new information comes to light or when new medicines are added to a list.

It is important to consider different dose forms too and classify them by the same system. Thus an injection of one drug could be "vital" but the tablet form or ointment or cream could be an "E" or even "N" classification.

How to Conduct a VEN Classification.

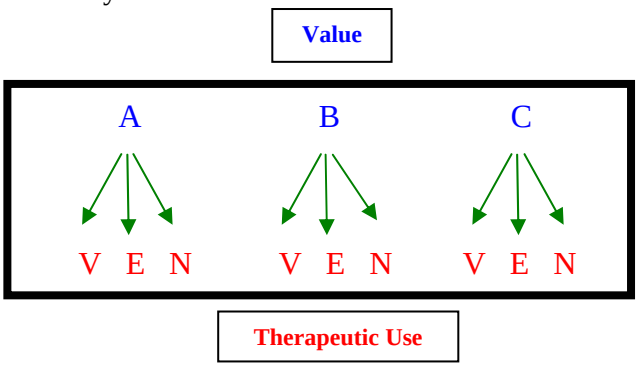
A pharmacist should make up a list of all the medicines to be categorised. This list should be circulated to all department heads for review. They should each pick out the medicines they believe are vital or essential. The process is easier and quicker if the pharmacist or drug and therapeutics committee (DTC) first assigns a "tentative" VEN category to each drug and its various dose forms and then asks the specialists to agree or disagree or ignore if they have no particular opinion about the drug. Because there will be some disagreement between specialties the completed drug lists should be collated and a consensus taken or the highest category noted should be accepted if it is justified.

The process and the need for it must be explained in detail to the specialists. The idea is best "sold" and accepted if the specialists are led to understand that this exercise will improve supplies and eliminate stock-outs and interruptions.

How to tell your A-B-Cs from your V-E-Ns?

What is the difference between ABC and VEN analysis? The easiest way to think about it is that ABC refers to the monetary value of a medicine or product whereas VEN refers to the actual therapeutic use of drugs.

Every drug in an inventory can be classified by both systems thus:



Both systems should be used for procurement by the central medical supplies department of a country. The system provides a logical means of rationalising medicine purchases. Thus N drugs in general and **AN** drugs in particular should be the lowest priority purchases in any health system

In developing countries where the allocated budget for medicine is limited this methodology has proven to be extremely useful and has helped to keep the supplies of medicine flowing smoothly.

However, the system is not just for poorer countries and is applicable to any procurement agency.

The following table is reproduced from an article on purchasing by WHO[4].

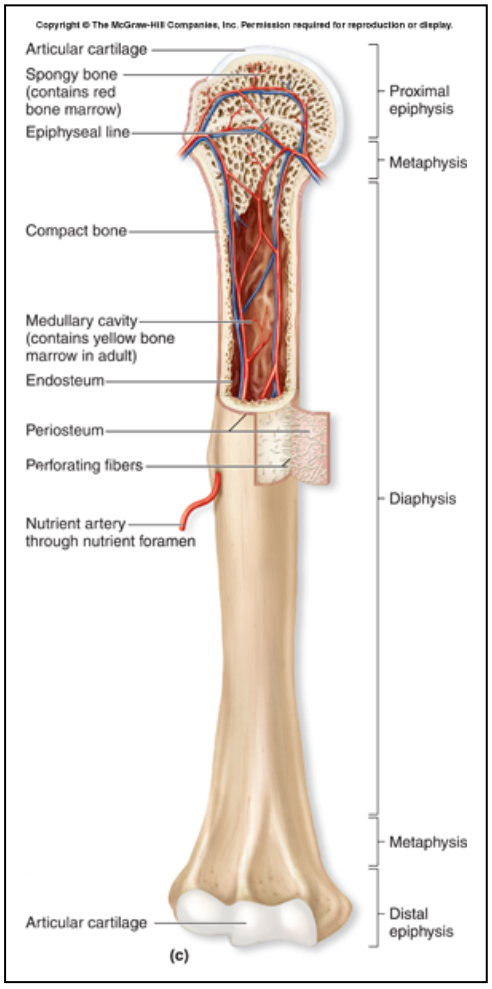
Effects of candidate medicines for purchase	**First...**	**Then...**
Different	Determine VEN category	Prefer vital to essential drugs, essential to non-essential
Similar	Determine VEN category and cost-effectiveness	Prefer vital to essential drugs, essential to non-essential Vital: prefer drugs that most reduce mortality Essential: prefer drugs that most improve quality of life Non-essential: prefer drugs that most reduce minor symptoms
Identical	Determine VEN category and cost	Prefer vital to essential drugs, essential to non-essential In each category: prefer the lowest-cost drug

Conclusion

Medicines should never be selected or procured depending only on the cost. An essential medicines list should be made on the basis of cost and therapeutic effectiveness. The list is established somewhat empirically based on criteria such as: diseases present in the country, the availability of skills and technical resources to make good use of drugs, the financial resources for medicine procurement, and whether drugs are manufactured within the country.

Which criteria govern drug selection will depend on national health objectives and the context in which the drugs are used.

Check Out This Site



Another very useful anatomy site to check is

http://academic.kellogg.cc.mi.us/herbrandsonc/bio201_McKinley/f6-4c_gross_anatomy_of__c.jpg

It is mainly devoted to skeletal structures.

[4] Guide to Drug Financing Mechanisms. http://www.who.int/medicinedocs/index.fcgi?sid=Q10rVtjd9ee80ca7000000004742e93f&a=d&d=Jh2928e.4.2.2

Single *vs*. Combination Products

❖ Products with single agents are preferable and allows more flexibility in prescribing and dosing

❖ A fixed-ratio combination product is accepted only if:

- the clinical literature justifies concomitant use of 2 or more drugs
- the therapeutic effect or safety is greater than the sum of the effects of each drug separately
- the cost is less than the sum of the cost of individual products
- the quality can be assured
- it meets the need of the majority of patients
- it improves patient compliance if deemed necessary
- it is effective in preventing emergence of resistance

Variations in Medicine Response

❖ Variability in the effect of a drug is a serious problem when it is used clinically.

❖ Variation in response can result in:

- lack of efficacy
- unexpected side effects

Variation in response may be due to one or more of the following:

- Medicine formulation
- Body weight, age, surface area
- Physiological and pharmacokinetic variable (drug absorption, distribution, metabolism and excretion)
- Pharmacodynamic variables
- Disease variables
- Genetic abnormalities
- Environmental variables
- Drug or food interactions

Information Capsules

Dr Ahmed Abdo-Rabbo & Ph Manal Al-Ansari

Public Beliefs on Medicines

People believe that:

❖ Medicines' efficacy is linked to colou symbolism **(Red medications, are thought to be good for the blood)**

❖ Medicine injected into the bloodstrean does not leave the body quickly & has stronger effect than administered orall

❖ Oral medicines like food, enter the digestive system and eventually leave the body through defecation

❖ New medicines are more effective

❖ Cheaper generic alternatives are ineffective

❖ Medicines produced by local manufacture have less effects and more side effects

❖ Herbal medicines are free from side effects

Essential Medicines Lists

❖ **Model List of Essential Medicines**

- Prepared by WHO Expert Committee
- Should be seen as a "guide list" in preparing National List
- Contains a limited number of medicines needed to take care of the common health problems

❖ **National List of Essential Medicines**

- Includes medicines necessary for the health needs of the majority of the country population
- Does not imply that no other medicines are useful
- Should be updated periodically e.g. every 2 years

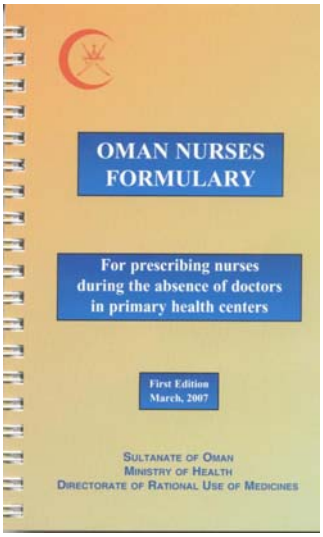
❖ **Institutional Essential Medicines List**

Institutional or Regional Essential Medicines Lists are used for a particular region or hospital

The Oman Nurses Formulary

Dr. Ahmed Abdo-Rabbo

Due to shortage of general practitioners, particularly in rural areas, as well as to enhance access to health care services, nurses in these areas have been given extra responsibilities. They are authorised to diagnose, prescribe from a limited list of medicines, treat the patients and, if necessary, refer to other practitioners.



This Oman Nurses Formulary, a nurse prescribers' formulary was recently prepared by the Directorate of Rational Use of Medicines. It is introduced to nurse prescribers in primary health care centres who are allowed to prescribe from the list of preparations issued by the Directorate General of Medical Supplies (DGMS) during the absence of doctors.

The formulary provides the nurse prescribers with independent and useful information from reliable scientific sources about the medicines relevant to their prescribing practice. It contains monographs on the medicines permissible for prescribing. Each monograph contains short clinically relevant information including the category of the medicine, its indication/s, cautions to be observed when using the medicine, contraindications, side effects, drug interactions, and dosage forms allowed to be prescribed, as well as patient information. The formulary is designed as a booklet of an appropriate size to be carried in the pocket for ready and rapid reference.

Nurse prescribers are not entitled to prescribe items which are not listed in the formulary.

It is recommended that non-proprietary names should always be used for prescribing the medicines. Also, the nurse prescribers should consider the clinical suitability and cost effectiveness when prescribing.

Extra education and training are required to be added to the nurse's basic training in order to achieve the goals of appropriate and rational prescribing. For this reason specialist workshops and training courses will be conducted very soon.

Finally, it is hoped that nurse prescribers will make use of the formulary and use the information effectively to provide better outcomes for the patients.

Drug Name Word Search Puzzle

Object: Find as many *genuine* drug names as you can in the grid below. Circle the name of the medicine found.
Be careful with the spelling! Only the current INN drug names as listed in BNF or ONF are acceptable as correct.
Note: The letters can be found diagonally, across or down the grid. Sometimes the word can read backwards (e.g. n i r i p s a = a s p i r i n)! Also some letters can be used in more than one drug name! There are a total of **19** drug names to be found including the one highlighted!

i	x	r	o	s	c	a	h	c	l	t	l	e	r	o	g	i	a	o	e
a	n	g	x	u	p	a	r	o	x	a	t	i	n	e	l	r	l	o	c
f	i	c	c	l	o	i	l	i	i	p	v	a	n	l	e	a	r	i	t
n	e	i	f	p	l	o	c	l	a	o	c	t	x	z	n	n	i	m	o
l	o	p	c	h	n	n	s	r	l	y	a	e	l	z	i	n	x	p	e
o	n	t	i	a	i	r	a	c	c	m	m	l	i	l	e	c	x	l	o
s	r	a	r	m	r	c	y	l	y	i	r	p	l	p	t	p	p	n	y
e	a	p	a	e	e	c	o	c	p	c	i	i	i	v	s	r	n	l	e
x	o	x	v	t	a	s	i	i	n	n	c	a	v	o	y	n	p	o	s
r	p	e	a	h	p	n	f	p	e	a	o	a	f	o	c	a	p	o	p
c	y	m	m	o	c	e	i	r	x	c	o	e	l	l	l	x	e	i	e
l	o	n	r	x	c	t	c	o	l	a	i	n	u	a	y	c	p	c	i
l	l	i	c	a	x	o	l	f	o	r	p	i	c	n	t	x	i	a	f
c	n	l	i	z	f	c	a	l	p	b	z	p	l	f	e	e	i	c	r
i	i	l	a	o	u	c	l	o	a	a	f	e	o	i	c	e	v	o	a
i	n	i	l	l	i	c	i	x	o	m	a	z	x	e	a	n	p	t	o
o	e	c	f	e	l	i	a	a	l	a	l	n	a	i	a	i	e	p	c
n	l	y	x	c	e	o	t	c	c	z	z	a	c	o	c	n	o	v	o
d	o	x	y	c	y	c	l	i	n	e	c	l	i	s	o	i	i	l	n
c	l	o	s	p	o	r	i	n	i	p	o	o	n	l	i	p	n	n	l
e	a	m	o	l	a	n	z	a	p	i	n	e	o	f	x	l	a	e	i
i	l	a	n	e	r	d	a	p	c	n	i	l	l	i	c	y	x	o	d
l	r	a	n	x	c	n	o	y	m	e	t	o	p	r	o	l	o	l	a

To get you started metoprolol has been highlighted in the above grid.
The easiest way to complete the puzzle might be to scan the page as a picture into a word processor like Word ® and then you can use the basic transparent shapes in the drawing tools toolbar to highlight the drug name. You can also rotate the shape to match the direction of the word too and even use different colours for the lines! Photocopy this article to save the magazine!

5 Correctly completed grids will be selected at random by the editor for a small prize.

For submission of articles or for questions about any article please contact:

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