Therapeutic and Toxic Potential of OTCs

– Prof AK Khare

Prof AK Khare

Head: Physiological Sciences
University of Zambia Medical School
PO Box 50110
LUSAKA
Zambia

Curriculum Vitae

Prof Khare was born in India in 1955. He graduated from Kanpur University (India) in 1977, and obtained a Doctorate in Medicine from the same University in 1981. He lectured in different medical schools in India and in Kathmandu (Nepal) and moved to Africa as senior lecturer in Dar-es-Salaam (Tanzania) and as Associate Professor in Colombo (Sri Lanka) and Harare (Zimbabwe). Prof Khare is currently Head of Physiological Sciences and a Consultant Physician to University Teaching Hospital in Lusaka, Zambia.

Acknowledgements:

I thank University of Zimbabwe Medical Librarian for assistance in updating information using Medline and Mrs M R Madyambudzi for typing meticulously.

Summary

A short historical development of drug regulations is given, illustrating how it came about that two drug groups are now available: those on prescriptions by registered practitioners only, and those available over-the-counter. The knowledge and attitude of doctors will determine whether OTCs have a positive or negative impact. Guidelines are given on how to select the appropriate OTC and the toxic potential in specific drug groups is highlighted. It is concluded that much is dependent on the doctor in this field, whether he is knowledgeable about the drugs and whether he recognises the greater and legitimate role currently played by sophisticated patients in making their own health care decisions.

S Afr Fam Pract 1993; 14: 390-396

KEYWORDS:
Drug Evaluation; Self Medication; Physician-Patient Relations.

In most countries, drug regulations divide medicines into two groups: those sold only on prescriptions from a registered medical practitioner, and those for which directions for safe use by the public can be supplied. The latter is termed 'Non-prescription' or 'Over The Counter' (OTC) drugs.

Until early in the 20th century, medical care was mostly provided by non professionals and patent medicines were the mainstay of therapy in most countries. In the early 20th century, pharmacology developed as a science, and scientific studies concluded that the matter of drug use by non-professionals cannot safely be left like that. During the time of the second world war, we had what is termed a 'Drug explosion'. It was the beginning of substantial government intervention in the field of medicine which paralleled the proliferation of drugs. Initially it was confined to safety aspects and was developed as issues arose, until the thalidomide disaster of 1961, when all governments worldwide extended their control of medicines not only to safety, but to other aspects like quality, efficacy and supply.

Official regulations forced newer synthetic medicines to be sold on prescription only once they were approved by drug regulatory agencies. However, markets are still flooded with over the counter drugs. In 1989, the American public spent approximately 10 billion dollars on an estimated 300 000 products representing 700 active ingredients in various forms and combinations. It means that many products are advertised in a way that it suggests there are significant differences amongst them. For example, there are over 100 analgesic products containing not more than a few active ingredients, made different from one another only by brand names which were chosen to suggest a specific use or strength ('feminine pain', 'extra', 'maximum'); or by special dosage forms (enteric coated,

... Therapeutic and Toxic Potential of OTCs

powders, sustained release)[1]. And, of course, there is a price attached to all these gimmicks. It is probably safe to assume that the public is overwhelmed by all these products presented, and will use the one most heavily and attractively advertised.

Recently, drug regulatory agencies have engaged themselves in the review of OTCs for safety and efficacy. The major aims of reviewers are elimination of ineffective or unsafe ingredients from OTC formulation, and making available more drugs as OTCs which were previously available on prescriptions only (eg Hydrocortisone ointment, ibuprofen etc). It is now agreed that self medication is appropriate where appropriate diagnosis is unnecessary, for relief of mild cases of some chronic or recurrent diseases (eg eczema) and when a drug has wide margin of safety.[2]

10 billion dollars spent in 1989 on OTCs in America

Why doctors should be familiar with OTCs

When drug regulatory agencies permit the sale of certain drugs for self medication or 'home use' without consulting a doctor, why then should doctors bother to familiarise themselves with OTCs? It is to help the patient select the most economical OTC from the plethora of these products. OTCs are effective against many common

Table 1. Some common ingredients of known efficacy in OTC preparations

Therapeutic Class	Ingredients (Doses)	Comments
Allergy	Chlorpheniramine (4mg x 4/day) Diphenhydramine (25-50mg. x 4/day) Chlorpheniramine (4mg) plus Pseudoephedrine Tripolidine (2,5mg) with pseudoephedrine (60mg) Tripoliding (2,5mg) with pseudoephedrine (60mg)	Antihistaminics alone relieve most symptoms of allergy. Chlorpheniramine is less sedating than Diphenhydramine and Tripolidine. Pseudoephedrine may counteract sedation. Persons should be cautioned against sedative effect and interaction with alcohol and CNS depressants.
Analgesics	Aspirin (300-600mg x 4/day) Paracetamol (500-600mg x 4/day) Ibuprofen (200-400mg x 4/day)	Addition of Antacid, caffeine and methapyrilline does not increase analgesic efficacy. Avoid products containing phenacitin. Use aspirin carefully in patients with peptic ulcer disease or bronchial asthma.
Antacids	Magnesium Hydroxide and Aluminium hydroxide mixtures (Gellusil Mylauta)	Less adverse effects. Na+ content is less. Liquid antacids have more acid neutralising capacity.
Cough Suppressants	Codeine (10-20mg x 4/day) Dextromethorphan (10-20mg x 4/day) Giuaifenesin (200-400mg x 4/day)	Addictive liability of codeine is low. Addition of expectorants is questionable. Giuaifenesin has least toxicity. Watch for other ingredients in these products.
Decongestants	Xylometazoline 1% nasal drops Phenylephrine 2% nasal drops Pseudoephedrine 60mg x 4/day oral Phenylpropanolamine 25mg x 4/day oral	Effective in symptomatic management of colds. Xylometazoline is longer acting. Oral agents may have systemic effect. Longterm use is undesirable. Use with care when other medicines given concurrently.
Laxatives	Bulk formers (Bran) (10-20g/d) Stool softners (Docussate sodium) (100mg x 2/day) Milk of Magnesia (1% soln. 2TSF/d) Phenolphthaline (60mg/d)	Bulk formers are safest for chronic use. Stool softners may be used as alternative. Chronic abuse should be discouraged.

ailments and may be cheaper than prescription drugs. Secondly, many ingredients in OTCs may actually worsen the existing problem or interact with drugs prescribed by the doctor (nasal decongestants and tricyclic antidepressant, MAOIs or antihypertensives). Thirdly, many OTCs have a potential for abuse (phenylpropanolamine has been sold as a cocaine substitute due to its sympathomimetic effects). Therefore, a general awareness of OTCs will enable the physician to recognise the therapeutic and toxic potential of these drugs.

Advertisements suggest significant differences in similar drugs

How to select OTCs

Table I lists examples of OTCs that may be used effectively to treat medical problems commonly seen in ambulatory patients. The selection of one ingredient over another, will depend upon the underlying disease and other medicines concurrently administered. I suggest some general guidelines to achieve therapeutic objectives with OTCs.

1. Select the product that is simplest in formulation with regard to ingredients and dosage form. In general, single ingredient formulations will be preferred. While some products contain effective doses of all ingredients in formulation, others contain therapeutic doses of one or two, but subtherapeutic doses of others. Furthermore, the onset and duration of the effect of different ingredients may differ to the disadvantage of the patient. There is always a possibility that some of the ingredients may not be known to the patient, or even the clinician. Aspirin, for example, may be an ingredient in cough mixtures and cold preparations while the patient may have a separate prescription for an analgesic dose of aspirin (or other analgesics).
2. Select a product which contains therapeutically effective doses. Some fixed dose formulations use more than one ingredient but in subtherapeutic dosage.
3. Select a product that lists its ingredients and the amount (or concentration). The label should be carefully read as the strength of the ingredients may be changed without notice to public, or change of brand name.
4. Always recommend a generic name if it is available. (eg paracetamol, acetyl salicylic acid). It will cost less to patient or hospital.
5. Do not be carried away by claims made by advertisements claiming specific superiority over other similar products.
6. For small children, dosage form and palatability of the product should be taken into consideration.

If these guidelines are followed and patients are helped to choose OTCs scientifically, the merits of self medication in minor illness can be retained, and of course, it will have economic consequences to the advantage of the community.

Sources of information on OTCs

Physicians can contact the Drug Information Service in their country, or consult the Physician Desk Reference (PDR-non prescription) or the Monthly Index of Medical Specialities (MIMS), which are published in most countries. The drug manufacturers will be able to supply information on various aspects of OTCs.

Toxic potential of OTCs

While OTCs have therapeutic potential due to the wide margin of safety and advantage of low cost, these should not substitute physician consultation of prescription drugs. Physicians should be aware that certain preparations should be avoided, or used with caution in selected patients, because they may exacerbate existing problems or interact with the drugs prescribed by the physician. Ingredients with greater toxic potential are 'hidden ingredients' in OTCs where we do not expect their presence. (Table II). This lack of awareness of these

Self medication can be appropriate

... Therapeutic and Toxic Potential of OTCs

Table II: Hidden ingredients in OTC preparations

Ingredient	OTC Preparations	Product Examples
Alcohol	Cough mixtures	Formula 44 (20%) Halls (22%)
	Cold preparations	Romilar (20%)
	Mouth washes	Listerine (75%)
Antihistaminics	Analgesics	Percogesic, Sinarest
	Asthma products	Brontin
	Cold remedies	Alkaseltzer plus, Benylin Dristan, Triaminic
	Skin preparations	Pyribenzamine Cream
	Motion sickness/ anti-emetic products	Dramamine, Marezine Bonine
Anti-muscarinic agents	Antidiarrhoeals	Donnagel
	Cold remedies	Sinulin
Aspirin and Salicylates	Analgesics	Alkaseltzer, Anacin, Aspro Aspro, persistin
	Cold preparations	Alka Seltzer plus, Dristan, Triaminic
	Menstrual products	Midol
	Sleep Aids	Tranquil
Caffeine	Analgesics	Anacin, Bromoseltzer, Excedrin, stanback
	Cold remedies	Dristan, Triaminicin
	Menstrual products	Midol
	Anorectics	Anorexin capsules
Local Anaesthetics	Cough remedies	Formula 44, Vicks cough discs
	skin creams	Nupercainal, Americaine
	Haemorrhoidal preparations	Americaine, Nupercainal
	Lozenges	Vicks lozenges
	Toothache remedies	Toothache drops
	Weight loss products	Diet trim tablets
Sodium	Analgesics	Alka seltzer, Bromoseltzer, sodium salicylates
	Antacids	Alkaseltzer effervescent antacids, ENO Fruit salt, soda mint tablets
	Cough mixtures	Dristan, Formula 44, Vicks cough mixture
	Laxatives	Fleets enema, Liver salts
Sympathomimetic	Analgesics	Allerest, Sinarest tabs.
	Asthma products	Bronkotabs, Tedral
	Cough mixtures	Formula 44, Triaminic
	Lozenges	Sucrets
	Menstrual products	Femcaps
	Topical	Vicks inhaler, Neo-synephrine
	Weight control remedies	Prolamine, Doxatrin

ingredients, and the belief of the physician that OTCs are 'ineffective' and 'harmless', may interfere with therapy.

Nasal decongestants, cough suppressant mixtures, appetite suppressants often contain sympathomimetics which should be avoided as far as possible in patients with hypertension, angina or hyperthyroidism. In fact, the possibility of overuse of these agents should be considered in differential diagnosis of hypertensive emergencies[3]. Ischaemic chest pain after the abuse of nasal decongestant has been reported.[4] Severe

Many ingredients in OTCs may actually worsen the existing problem

hypertension, secondary to nasal decongestant has also been reported.[5] 'Bron', an OTC cough mixture in Japan, was associated with hallucinatory paranoid syndrome in 44 abusers.[6] This mixture contained methylephedrine, codeine, caffeine and chlorpheniramine. It was suggested that methylephedrine and codeine were responsible for this affective disorder. Twenty (20) reports in Australia, Belgium and the Netherlands have implicated that oxalamines containing cough mixtures were the cause of hallucinations in children.[7] (Perhaps high doses for small children). Cough mixtures containing iodine

have been reported to have caused thyrotoxicosis.[8,9]

Pain killers are used very often; paracetamol may cause serious hepatotoxicity. It is one of the most common drugs children accidentally ingest and it is often stored in unsafe medicine chests. Fortunately

Select the simplest drug; a single ingredient formulation

children are less prone to toxic effects of paracetamol and only a few fatalities are reported.[10] It should be noted that alcoholics are very prone to hepatotoxic effects of paracetamol in whom toxicity develops even when they are taking therapeutic doses.[11,12] In pregnant women, chronic paracetamol use may cause maternal hepatotoxicity and intracranial haemorrhage at the time of delivery (increased coagulation time)[13]. In a sizeable number of paracetamol abusers, non ulcer dyspepsia may be seen.[14] Dangers of aspirin, especially its toxic effect on gastro-intestinal haemorrhage and its ability to cause wheezing in asthmatic patients, are well recognised. While aspirin protagonists recommend prophylactic use of aspirin in the elderly population with clinically evident coronary artery disease[15], it should be restricted in children below 12 years. In USA, the media played a central role in changing the use of aspirin among children with viral illnesses following report of its association with Reye's syndrome, (a rare but delay disease)[16]. Practitioners may successfully change consumer behaviour on such reports. Hypertensive patients may be warned that ibuprofen, now an OTC, may elevate the blood pressure if consumed in maximum doses for more than a few days.[17] A Boston collaborative drug surveillance program did not report anatomic or pathologic findings associated with analgesic nephropathy. They concluded that renal disease attributable to OTC analgesics, is rare.[18] However, considering the massive use of OTC analgesics, it requires a quantitative assessment of the risk involved. It may be noted here that OTC analgesics containing phenacetin, are reported to be associated with increased risk of hypertension and renal disease.[19] Codeine, an important ingredient of some OTC analgesics, has a small abuse potential, though it has been

Select a product that lists its ingredients and the concentrations

reported to be associated with obsessive compulsive disorders.[20] Caffeine (often combined in analgesic mixtures), does not significantly affect blood pressure or increase the risk of cardiovascular disease.[21] However, it may cause rebound headache.[22] It has an association with fibrocystic disease of the breast.[23]

Antacids are often taken for relief of dyspepsia. They have a variable amount of sodium which may increase the risk of sodium retention in oedematous states and hypertension. Aluminium containing antacids can deplete phosphates and occasionally may cause renal stone

Recommend a generic name if possible

disease[24]. Chronic use of antacids, milk and cream etc may cause milk alkali syndrome. Antacid induced diarrhoea is common.

Anorectics: Phenyl propanolamine is considered safe and effective in weight reduction provided it is used on a short term basis (12 weeks).[25] Serious side effects are infrequent.

Laxatives: are mostly abused by elderly people. Liquorice containing laxatives have been reported to have caused pseudohyperaldosteronism, a diagnostic problem in hypertension.[26] Laxatives should be discouraged for reducing weight. Senna is perhaps the most harmless nonfiber laxative. Patients may be warned that chronic laxative use may cause water and electrolyte imbalance. With a fibre type laxative, adequate water intake must be ensured to avoid abdominal cramps or intestinal obstruction. Overuse indicates that the public does not know the best, and needs advice and education.

Antihistamines: used in cough and cold remedies, are mostly sedative

and interact with alcohol and other CNS depressant drugs. Patients taking these, should not drive or operate machinery. Cetirizine, Revocaastine, Terfenadine and Astemizole are second generation antihistaminics which are non sedating.

Vitamins and micronutrients: are often taken by patients without realising that these can exert pharmacological effects. These are mostly taken by the elderly who take a maximum number of other drugs as well, and have the greatest incidence of chronic illnesses. Physicians may help selecting a preparation supplying RDA of vitamins and minerals. The attractive colour of such tablets (or capsules) is often the cause of accidental ingestion in children.[27]

Topical preparation: Education of the public is important for the use of eye drops. Some cases of blindness have been reported because OTC eye drops were used.[28] Diabetic patients

Patients play a greater role today in their health care decisions

should not use 'corn caps' as some patients reportedly developed ulceration.[29] Topical formulations containing antihistaminics, local anaesthetics, antimicrobials, deodorants and preservatives, may sensitise the skin and cause allergic reactions.

OTCs in pregnancy: Drug use in pregnancy is common. A Glasgow study[30] found that 34,8% of the women who took a medication, used 150 drugs from 35 drug groups. While there is a public concern about drug use in pregnancy, the fact remains that drugs are still widely used, and much more systematically gathered information about consequences of OTC use in pregnancy is needed.

Get a complete drug history (including OTCs) at the first consultation

Conclusion

Despite the widespread use of OTCs, the incidence and frequency of serious toxicity from these agents, is low. The most unwanted reactions are predictable, mechanism based and are dose related effects due to drug use in improper settings, excessive dose or interactions with prescription or other OTC drugs.

The attitudes of physicians will largely determine whether OTCs will have a positive or negative impact on the therapeutic contract. In one study, a group of physicians knowing that aspirin is as effective as proprietary nonsteroidal anti-inflammatory analgesics (and much cheaper), actually prescribed the latter almost six times more often than aspirin.[31]

Physicians should recognise the legitimate role of OTCs in the current environment where sophisticated and busy patients play a greater role in their own health care decisions. On first encounter with the patient, a complete drug history including OTCs, must be obtained and updated at subsequent visits. In an era when cost considerations are greater than before, OTCs should be considered and decided upon when they will be appropriate alternatives to prescription medicines.

References:

1. Physician's Desk Reference for Non prescription Drugs. 13th Ed. 1992: Medical Economics.
2. Handbook of Non prescription Drugs. 9th ed. American Pharmaceutical Association: 1990.
3. Heyman SN, Mevorach D, Gihanem J. Hypertensive crisis from chronic intoxication with nasal decongestant and cough medication. DICP 1991; 25(10): 1068-70.
4. Whittet HB, Veitch D. Ischaemic chest pain after abuse of nasal vasodilator. BMJ 1989; 299: 860.
5. Leon-Santroma M, Gil I, Nogues I, Rivera A. Severe hypertension secondary to nasal decongestants. Atencion Primaria 1991; 8(2): 158.
6. Ischigooka J, Yochida Y, Murasaki M. Abuse of BRON: a Japanese cough suppressant solution containing mechyl-ephedrine, codeine, caffeine and chlorpheniramine. Progress in Neuropsychopharmacology and Biological Psychiatry 1991; 15(4): 513-21.
7. McEwen J, Meyboom R H, Thijs I. Hallucinations in children caused by oxalamine citrate. Med J Australia 1989; 150(8): 449-50.
8. Huseby J S, Bennett S W, Hagensee M E.

... Therapeutic and Toxic Potential of OTCs

Hyperthyroidism indiced iodinated glycerol. Amer Rev Resp Dis 1991; 177(6): 1703.

9. Drinka P J, Nolten P W E. Effects of iodinated glycerol on thyroid function studies in elderly nursing home residents. J Amer Geriat Soc 1988; 36(10): 911-3.

10. Penna A, Buchnan N. Paracetamol poisoning in children and hepatotoxicity. Brit J Clin Pharmacol 1991; 32(2): 13-9.

11. Rex D K, Kumar S. Recognising acetaminophen toxicity in chronic alcoholics. Postgrad Med 1992; 91(4): 241-5.

12. Kumar S, Rex D K. Failure of physicians to recognise acetaminophen hepatotoxicity in chronic alcoholics. Arch Int Med 1991; 151(6): 1189-91.

13. Kurzel R B. Can acetaminophen result in maternal and fetal hepatotoxicity? S Afr Med J 1990; 83(8): 953-5.

14. Talley N J, NcNeil D, Piper D W. Environmental Factors and chronic unexplained dyspepsia. Association with acetaminophen but not other analgesics, alcohol, coffee, tea or smoking. Dig Dis Sci 1988; 33(6): 641-8.

15. Dalen J E, Gioldberg R J. Prophylactic aspirin and the elderly population. Clin Geriat Med 1992; 8(1): 119-26.

16. Soumerai S B, Ross-Degnan D, Kahn J S. Effects of professional and media warnings about the association between aspirin use and Reye's syndrome. Milbank Quart 1992; 70(1): 155-82.

17. Bradley J G. Non prescription drugs and hypertension. Which ones affect blood pressure? Post-grad Med 1991; 89(6): 195-7.

18. Derby L E, Jick H. Renal parenchymal disease related to over the counter analgesic use. Pharmacotherapy 1991; 11(6): 467-71.

19. Dubasch V C, Rosner B, Sturmer T. An epidemiological study of analgesic drugs. New Eng J Med 1991; 324(3): 155-60.

20. Senjo M. Obsessive compulsive disorder in people that abuse codeine. Acta Psych Scand 1989: 79(6): 619-20.

21. Myers M G, Harris L. High dose caffeine and ventricular arrhythmias. Canad J Cardiol 1990; 6(3): 95-8.

22. Fennely M, Galletyly D C, Purdie G I I. Is caffeine withdrawal the mechanism of post operative headache? Anaesth Analgesia 1991; 72(4): 449-53.

23. Rohan T E, McMichael A J. Methyl-xanthines and breast cancer. 1988; 41(3) 390-3.

24. Harmelin D L, Martin F I. Antacid induced phosphate depletion and nephrolithiasis. Austr N Z J Med 1990; 20(6) 803-5.

25. Williams D M. Phenylpropanolamine hydrochloride. Amer Pharm 1990; 10: 47-50.

26. Scoli M, Pratesic, Sennaro M C, Zampollo V, Armanini D. Pseudohyperdaldosteronism from liqorice containing laxatives. J Endocrin Invest 1990; 13(10): 847-8.

27. Dean B S, Krenzelok E P. Multiple vitamins and vitamins with iron: accidental poisoning of children. Veter A Human Toxicol 1988; 30(1): 23-5.

28. Rumelt M B. Blindness from misuse of over the counter eye medications. Ann Ophthal 1988; 20(1): 26-7.

29. Watkins P J. Corn cures can damage your feet: an important lesson from diabetic patients. Diab Med 1989; 6(9): 818-9.

30. Epstein A U, Read J L, Winickoff R. Physician beliefs, attitudes and prescribing behaviour for anti-inflammatory drugs. Am J Med 1984; 77: 313-18.

31. Rubin P C, Craig G F, Cavin K, Summer D. Prospective survey of use of therapeutic drugs, alcohol and cigarettes during pregnancy. Br Med J 1986; 292: 81-3.