

Irrational drug combinations: Need to sensitize undergraduates

Prescribing fixed dose drug combinations has become the “in thing” in medical practice. Using the excuse of better patient compliance, many doctors, both in private as well as government prescribe irrational fixed dose drug combinations. Quite a few infectious diseases are becoming resistant to treatment with a single drug. With the escalating cost of drugs, there is poor drug compliance, which further magnifies the problem, both for the prescriber as well the patient. Manufacturers of drugs having quickly tuned in to the potential golden egg, are marketing fixed dose drug formulations for various diseases.

Even though use of combinations of drugs is common practice, the selection of optimal dose and optimal combination has remained largely a matter of trial and error. The basis of many fixed dose drug combinations being taught to the undergraduate medical students and also being prescribed popularly, appears to be irrational to pharmacologists.

CIMS lists more than 100 irrational combinations which are not approved in any developed country but are being

marketed in India. This fact has to be taught to undergraduate medical students in their formative years of learning so that once they address medical ailments like malaria, tuberculosis, AIDS, hypertension, etc. they should be more logical in selecting appropriate drug combinations and should not be swayed by marketing tricks and false claims made by the pharmaceutical industry. The pharmacological basis of combining each ingredient in the formulation should be taught. Selection of P drugs, rational drug use, use of rational drug combinations and ethical laboratory practices should be inculcated in the student’s curriculum during their clinical training.

Fourteenth WHO model list of essential medicines (March 2005) contains only 18 approved drug combinations, whereas in India, there are innumerable examples of irrational drug combinations, which are easily available and can be bought without necessarily giving a prescription. [Table 1] This issue has to be urgently addressed by us, pharmacologists, as the magnitude of the problem is increasing.

Table 1

Some irrational fixed dose drug combinations available in the Indian market

Combinations	Irrationality
1. Norfloxacin + Metronidazole; Norfloxacin + Tinidazole; Norfloxacin + Tinidazole + Loperamide; Norfloxacin + Tinidazole + Dicyclomine; Norfloxacin + Ornidazole; Ciprofloxacin + Tinidazole; Ofloxacin + Tinidazole; Ofloxacin + Metronidazole; Ofloxacin + Ornidazole; Gatifloxacin + Ornidazole.	Though claimed to be broad spectrum, combining (antiamoebic) with fluoroquinolone (antibacterial) is irrational because patient suffers only from one type of diarrhoea. Using this combination adds to cost, adverse effects and may encourage resistance.
2. Nimesulide + Diclofenac; Nimesulide + Dicyclomine + Simethicone; Nimesulide + Paracetamol; Nimesulide + Cetirizine + Pseudoephedrine; Nimesulide + Paracetamol + Tizanidine.	Nimesulide a controversial drug, has been banned in many countries. It is a sorry state of affairs that its combinations are readily available over the counter. Combining two NSAIDs may increase the side effects of both the NSAIDs. There is little documentary evidence that a preparation containing more than one analgesic is more effective than a single ingredient preparation.
3. Amoxicillin + Cloxacillin	Amoxicillin is inactive against staphylococcus, as most strains produce β -lactamase and cloxacillin is not so active against streptococci. For any given infection, one of the components is useless but adds to cost and adverse effect. Since amount of each drug is halved, efficacy is reduced and chances of selecting resistant strains is increased.
4. Domperidone + Rabeprazole; Domperidone + Esomeprazole	Increased incidence of rhabdomyolysis.
5. Simvastatin + Nicotinic acid; Atorvastatin + Nicotinic acid	Probability of myopathy is increased.
6. Roxithromycin + Ambroxol; Ciprofloxacin + Ambroxol; Gatifloxacin + Ambroxol; Cefadroxil + Ambroxol; Cefixime + Ambroxol + Lactobacillus	Many trials have failed to show superior efficacy of the combination over use of ambroxol alone in respiratory tract infection. Gatifloxacin is withdrawn.
7. Fluconazole + Tinidazole; Doxycycline + Tinidazole; Tetracycline + Metronidazole	Combining two antimicrobial agents to increase the spectrum of activity is irrational, as the patient may need only one drug. The keypoint is to make a correct diagnosis.
8. Enalapril + Losartan	Combining two drugs affecting the same pathway is irrational; it doesn't add to efficacy.
9. Cetirizine + Phenylpropanolamine + Dextromethorpan Cetirizine + Phenylpropanolamine + Paracetamol; Levocetirizine + Paracetamol + Phenylpropanolamine.	Phenylpropanolamine is a banned drug; yet it is a part of many cough and cold remedies. Besides its potential to cause stroke (more so in hypertensives), it can aggravate diabetes, glaucoma and prostate enlargement.
10. Diazepam + Dried aluminium hydroxide gel + Aluminium glycinate + Oxyphenonium; Diazepam + Magaldrate + Oxyphenonium; Diazepam + Dried aluminium hydroxide gel + Magnesium trisilicate + Dimethylpolysiloxane.	Antacids raise the gastric pH and reduce the absorption of benzodiazepines.
11. Cisapride + Omeprazole; Mosapride + Pantoprazole ; Ondansetron + Pantoprazole.	In patients with gastroesophageal reflux disease, the use of this combination has shown no benefit due to the addition of prokinetic drugs.

What needs to be done?

1. The hit and trial method of combining drugs should be replaced by a rational and logical basis for bringing out a fixed dose drug formulation. Operational, statistical and mathematical models constitute a highly versatile framework for mechanism based modeling (pharmacokinetic/ pharmacodynamic) by taking signal transduction properties of the drug combination into account. Sound scientific research should underlie the development and production of drug combinations.
2. There is a need to carefully monitor and censor misleading claims by the pharmaceutical industry. Some degree of irresponsibility on the part of the pharmaceutical industry and lack of vigilance of government agencies underlies the increased popularity of irrational drug combinations. Most advertisements in many of the medical journals published from India fail to mention important details pertaining to correct usage of drug combinations. Clinical pharmacists can play an important role in guiding and imparting knowledge to the public.
3. There is a need to strengthen the mechanism for continuing professional development of practitioners to ensure that they have the necessary knowledge and skills to prescribe rationally. Perhaps the insistence that prescribers, especially those in private practice should undergo a continuing medical education (CME) course once in two years on newer drug combinations, new drug molecules introduced into the market and adverse drug reactions will go a long way in curbing irrational prescribing.

4. ADR reporting should be made mandatory as they are in developed countries. Pharmacovigilance should be more effective.
5. Hospitals should constitute drugs and therapeutics review committees to rationalize prescribing.
6. Finally, medical schools and postgraduate colleges must take the responsibility of training students and young doctors how to assess new drug combinations more logically.

Unless we encourage our students to think rationally and independently this menace will continue to grow. We cannot complacently offload all blame onto the industry and government regulators; the onus of responsibility lies heavily on the shoulders of academicians too.

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