

Rational Drug Therapy

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Rational Drug Therapy

Enormous progress has occurred after 1940 in the field of drug development. Large numbers of drugs are available in market. "A pill for every ill" has become an accepted cultural norm. There is a need to rationalize use of medicines because several times use of the drug is unnecessary, irrational and harmful. According to W.H.O. - "Rational use of drugs requires that patients receive medication appropriate to their clinical needs, in doses that meet their own requirements for an adequate period of time and the lowest cost to them and their community".

The key of rational drug prescribing is -

To use

Right drug
In right patient
At right time
In right dose
By right route
With right documentation

Criteria for Rational Prescribing.

Rational drug prescribing refers to prescription of drug on the basis of -

Appropriateness - After correct diagnosis, the doctor has to decide whether the drug is actually needed or not. Functional constipation, prehypertension without compelling indications, vomiting during early pregnancy and early type 2 diabetes mellitus are managed by non pharmacological measures or life style modifications and if that fails then the drug is started.

Efficacy - Doctor must use a drug of adequate efficacy, by an appropriate route of administration and for proper duration For example -

For anti-inflammatory purpose - Ibuprofen is preferred over Paracetamol.

For anti-inflammatory purpose	Ibuprofen is preferred over Paracetamol.
For controlling tremors	Propranolol is preferred over Atenolol.
For anaerobic infection	Mtronidazole, Clindamycin, Chloramphenicol, Cefoxitin or Cefotetan are preferred over Vth Generation Cephalosporins and newer Aminoglycoside antibiotics.
For motion sickness	Promethazine is preferred over Prochlorperazine and Metoclopramide
For drug induced Parkinsonism	Benzhexol is preferred over Levodopa.
For stable heart failure	Metoprolol, Bisoprolol or Carvedilol is preferred over other β -blockers.

Safety - Drugs should be cautiously used in children, elderly patients, in presence of liver and kidney diseases. Cotrimoxazole should not be used during late pregnancy and under 2 months of age. Fluroquinolone antibacterials are used in prepubertal children if benefits outweigh the risk. Children are more prone to develop acute dystonia following the use of Metoclopramide. Use of Aspirin in children and adolescent suffering from chickenpox or influenza may cause Reye's syndrome. Drugs with ant cholinergic property should be avoided in elderly male. Effectiveness of both β_2 agonists and β blockers is reduced in elderly patients. During pregnancy the safe antibacterial drugs are Penicillins, Cephalosporins and Erythromycin, but Fluroquinolones, Aminoglycoside antibiotics, Tetracycline and Chloramphenicol should be avoided. The safe analgesic and antipyretic drug during pregnancy is Paracetamol. Hypertension during pregnancy is managed by Hydralazine, Methyldopa or Labetolol. Hyperthyroidism during pregnancy is managed by Propylthiouracil. Aspirin should be discontinued 2 weeks prior to due date of delivery otherwise there is an increased

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risk of post partum haemorrhage and premature closure of ductus arteriosus. Drugs like Doxycycline, Pefloxacin, Ceftriaxone, Cefepiderazone, Digitoxin are considered safe during renal insufficiency. If level of ALT is more than 3 times of its normal then preferred antitubercular drugs are Streptomycin and Ethambutol, while INH, Rifampicin and Pyrazinamide are to be discontinued.

Cost of Therapy -

Cost of therapy includes -

Direct cost of purchase of drug.

Cost involved in administration of drug.

Cost involved in monitoring of adverse effects (liver function test, renal function test, electrolyte level, ocular examination etc.)

Cost involved in treatment of ADRs.

Cost of treatment failure.

Expenses involved in visiting the hospital for administration of drug (with travel expenses loss of working hours should also be considered).

Therefore financial implications of drug therapy must be taken into consideration before selecting the drug. High cost of therapy adversely affects the compliance to therapy in developing countries. The incomplete treatment not only causes therapeutic failure, but also leads to emergence of resistant organisms (in case of infections). Therefore if equally effective and toxic drugs are available, the least expensive drug must be prescribed.

Determinants of Irrational Drug Use and Prescribing

These are -

1. Wrong choice of drug or incorrect use of drug

Drugs should be judiciously selected.

Following are the few examples of wrong choice of drugs -

Antibiotics - In every case of fever.

Antibacterials - In viral infections.

Antitussives - In productive cough.

Furosemide - In essential hypertension.

Loperamide - In infective diarrhoea.

Hydrochlorothiazide - In acute pulmonary oedema.

Intravenous Dextrose - In hypovolumic shock.

Phenytoin - In absences.

Nifedipine (alone) - In unstable angina and threatened MI.

Fexofenadine - In motion sickness and drug induced extrapyramidal toxicity.

2. "Me too" drugs - Availability of large number of drugs

is one of the important determinant of its irrational use. About 70% drugs are not absolutely necessary. Essential medicines are drugs which satisfy health care needs of majority of population and must be available at all the places, in adequate amount, all the times, in appropriate dosage forms and at affordable cost. 19th essential medicine list of W.H.O. (2015) contains 409 drugs including 28 fixed dose drug combinations. List of essential medicines updated in India in 2015 contains 376 drugs including 24 fixed dose combinations.

3. Self medication or OTC - Taking the drug without doctor's prescription, not having adequate knowledge of drugs and drugs dispensed by pharmacists without prescription of doctor are important determinants of irrational use of drug.

4. Prescribing by unqualified persons - Sometimes allopathic drugs are prescribed by practitioners of traditional system of medicine who are not well aware about efficacy and safety of allopathic drugs. Hon'ble Supreme Court in the judgement of a case - Poonam Verma V/s Ashwini Patel and others has clearly ruled that a person can prescribe drugs of only that system in which he is qualified and registered. If he prescribes the drugs of other systems, then he will be considered quack and deemed to be negligent *per se* without any further proof or argument.

5. Busy doctor - The doctor is too busy to imply his or her knowledge and discretion in selection of the drug. There is a possibility of either arrogance or ignorance.

6. Repeat prescription - Some doctors without regular review of patient, issue repeat prescriptions. There are instances where prescriptions were issued by receptionist without consultation of doctor.

7. Prescribing with intention to impress the patient and attendants - In order to obtain quick and intense effect from drug and to impress the patient and attendants, the doctor may prescribe the drug in high doses; however there is a risk of toxicity in this. Many times steroids are unnecessarily used with same intention.

8. Prescription influenced by patient - Sometimes doctor prescribes the drug at a request of patient, though it may not be required in patient. Doctor may succumb to pressure of patient for giving injection or IV fluid though these may not be required.

9. Prescription with misconcepts - Sometimes doctor prescribes the drug with following misconcepts -

(i) Newer drugs are always the better drugs - This is not always true. Limited knowledge is available at the time of marketing of new drug. Complete adverse effect profile of a new drug and its exact place in therapeutics are evident only after several years of use in population. Newer antibiotics are not the answer to every infection. IV

generation cephalosporin (Cefepime, Cefpirome) are not effective against listeria, enterococci, methicillin resistant staphylococci, Penicillin resistant pneumococci, B.fragilis, M.tuberculosis and M.avium complex. 7th generation cephalosporins (Ceftabiprole, Ceftaroline) are not much effective against anaerobic bacteria.

- Tigecycline is not effective against pseudomonas,
- Teicoplanin is effective against methicillin resistant staphylococci, but against methicillin sensitive staphylococci it is inferior to cloxacillin.
- Amoxicillin-Clavulanic acid combination is not effective against Pseudomonas.
- Tazobactam does not increase efficacy of Piperacillin against Pseudomonas and therefore, Tazobactam-Piperacillin combination offers no advantage over Piperacillin alone.
- Betaxolol though having better safety profile in asthmatics and COPD patients but is less effective than Timolol in chronic simple glaucoma.

(ii) Costly drugs are the better drugs- Some doctor prescribe the drug with notion that effectiveness of drug is directly proportional to the cost of drug. This is not always true. Uncomplicated UTI responds very well to Cotrimoxazole, Norfloxacin, Ciprofloxacin, Ofloxacin, Cephalaxin and Nitrofurantoin while expensive 3rd generation cephalosporins and newer aminoglycoside antibiotics should be reserved for complicated UTI. Expensive higher class of antibiotics offer no advantage over economical Cefazolin in prophylaxis of surgical site infection. Economical Thiazide diuretic is very effective antihypertensive drug in black, elderly and obese population.

(iii) Polypharmacy is more effective- Longer the prescription, more will be the academic excellence of the doctor is a wrong notion. Prescribing one drug for every symptom of disease without scientific justification represents the irrational use of drug. Polypharmacy increases the risk of ADRs, drug interactions, cost of therapy and may make diagnosis difficult sometimes. However, Polypharmacy is justified in complex clinical conditions and during emergency. Empirical antibiotic Polypharmacy is indicated in polymicrobial infections (like intra-abdominal abscess, lung abscess) and in life threatening infections (like meningitis, septicaemia etc.). Polypharmacy is also indicated in management of chronic infectious diseases like Tuberculosis and Leprosy.

(iv) Brand name drugs are better than generic name drugs - Generic or non-proprietary prescribing offers uniformity, convenience, economy and comprehension. As far as efficacy is concerned, there is no difference between branded drugs and their generic equivalents in 90% cases

despite of vehement claims of superiority of branded drugs by pharmaceutical industry.

(v) Fixed dose drug combinations are always superior - This is not always true. There is a possibility that one of the ingredients present in fixed dose combination may not be needed in patient or rather contraindicated. Dose of one drug cannot be changed without altering the dose of other. If adverse effect occurs with FDC, then it is difficult to ascertain which ingredient of FDC is responsible for the adverse effect.

W.H.O. essential drug list (2015) contains only 28 FDCs.

Essential drug list of India (2015) contains only 24 FDCs.

FDCs ENLISTED IN EML (National & WHO-2015).

- Amoxicillin + Clavulanic Acid.
- Imipenem + Cilastatin
- Sulfamethoxazole + Trimethoprim.
- Piperacillin + Tazobactam
- Artemether + Lumefantrine.
- Artesunate + Amodiaquine.
- Sulfadoxine + pyrimethamine.
- Artesunate + Mefloquine.
- Artesunate + Sulfadoxine + pyrimethamine.
- Efavirenz + Emtricitabine + Tenofovir.
- Emtricitabine + Tenofovir.
- Lamivudine + Nevirapine + Stavudine
- Lamivudine + Nevirapine + Zidovudine.
- Lamivudine + Zidovudine.
- Lopinavir + Ritonavir (LPV/R).
- Atazanavir + Ritonavir
- Tenofovir + Lamivudine
- Tenofovir + Lamivudine + Efavirenz
- Stavudine + Lamivudine
- Ledipasvir + Sofosbuvir
- Ombitasvir + Paritaprevir + Ritonavir
- Abacavir + Lamivudine
- Isoniazid + Rifampicin.
- Isoniazid + Ethambutol.
- Isoniazid + Pyrazinamide + Rifampicin.
- Ethambutol + Isoniazid + Rifampicin.
- Ethambutol + INH + Pyrazinamide + Rifampicin.

- Ethinylestradiol + Levonorgestrel.
- Ethinylestradiol + Norethisterone.
- Estradiol Cypionate+Medroxyprogesterone
- Levodopa + Carbidopa.
- Lidocaine + Epinephrine (Adrenaline).
- Prilocaine + Lignocaine.
- Oral Rehydration Salts.
- Glucose with Sodium Chloride.
- Ferrous Salt + Folic Acid.
- Budesonide + Formoterol.
- DPT + Hib + Hep B vaccine

Rational Drug Combinations not enlisted in essential medicine list

- Ergotamine + Caffeine in Migraine
- Aluminium Hydroxide + Magnesium Hydroxide as Antacid.
- Potassium losing Diuretic (Furosemide, Benzthiazide) + Potassium sparing Diuretic (Spironolactone, Triamterene) for hypertension and Heart failure
- β -Blocker or ACE Inhibitor or ARB + Thiazide Diuretic for hypertension and Heart failure
- Atovaquone + Proguanil in Malaria

SOME IRRATIONAL FDCs MARKETED IN INDIA FOR MANY YEARS

- Antiamoebic + Antibacterial Drug or Antifungal Drug
- Ampicillin/Amoxicillin + Cloxacillin.
- Antibacterial + Mucolytic Agent or Lactobacillus or Serratiaopeptidase.
- Piperacillin+Tazobactam(Against Pseudomonas)
- NSAID + NSAID or Antispasmodic or Muscle relaxants or PPI or Serratiopeptidase.
- Domoperidone + H2 Blockers or PPI.
- Ondansetron + H2 Blockers or PPI
- H2 Blockers + Antispasmodic Drug.
- Antacid + Antianxiety Drug or Antispasmodic or Anticholinergic Drug or H Blockers.
- Antidepressant with Antianxiety drug
- Antipsychotic with Anticholinergic Drug.
- Autussive + Expectorant + Mucolytic + Decongestant
- Leukotrine Antagonist + Levocetizine or Bambuterol
- Glimeperide + Pioglitazone + Metformin

Ministry of Health & Family Welfare, Govt. of India has recently banned 344 such irrational FDCs through a gazette notification.

Promotion of drug - Pharmaceutical industry may induce the doctor to prescribe its brand name drug on the basis of attributes other than efficacy and safety. Many times unethical and unhealthy tactics are practiced by pharmaceutical industry to promote the sale of their product.

Lack of drug information - One of the important determinants of irrational drug prescribing is lack of drug information. There must be provision to provide unbiased, updated and independent information about the drug. Information provided by the pharmaceutical industry may be biased in the favour of its marketed product.

Mistake by dispenser - like-

- Wrong interpretation of prescription by pharmacist.
- Supply of wrong drug from stock by pharmacist.
- Supply of wrong doses by pharmacist. Reglan (Repaglinide) may be dispensed in place of Reglan (Metoclopramide)

Impact of irrational use of drugs - Irrational use of drug may have deleterious effect on society as a whole and on health care delivery system.

Important consequences are -

Reduction in quality of drug therapy leading to increased morbidity and mortality.

- Increased cost of therapy.
- Increased risk of adverse effects.
- Unjustified psychological impact on patient that there is a pill for every ill and this may lead to increased demand of drugs.

Responsibility for promotion of rational drug therapy

Lies on -

(i) Drug control authority -

- To prepare, circulate and update essential drug list.
- Discourage irrational drug combination.
- Formulate guidelines for use of specific group of drugs like antibiotics, antihypertensive etc.
- Formulate guidelines for promotional literature.
- To make arrangement for rapid dissemination of ADR reports.

(ii) Teaching institution -

- To hold CME (Continuing medical education).
- To include training on rational use of drug in curriculum for both undergraduate and postgraduate medical students.

(iii) Industry -

- Be ethical while promotion of drugs.
- Assist in PMS (post marketing surveillance)
- To support drug awareness programme.

(iv) NGOs (Nongovernmental organisations)

- To make people aware of rational use of drug.
- To highlight discrepancies.

(v) Patients -

- Observe compliance to prescription strictly.

Concept of Essential Medicines

Essential Medicines are -“The drugs that satisfy the healthcare needs of majority of the population, they should therefore be available at all times, in adequate amount, at all the places, in appropriate dosage form and at affordable cost.”

India has prepared its first national essential Medicine list in 1996 containing 279 drugs to meet the common contemporary health needs of the general population of the country at that time. The list was revised in 2003, 2011 and then in 2015. W.H.O. has also published 19th list of essential medicines in 2015 which contains 409 drugs and other items including 28 FDCs. National essential medicine list (2015 contains 376 drugs including 24 FDCs). After identifying the diseases prevalent in majority of population, a multidisciplinary committee will select the essential medicines on the basis of Efficacy, Safety, Cost, Ease of administration, Local availability and Storage facility. Drug in list is mentioned by Non-proprietary name. There should be provision to assure the quality of essential medicines and also to provide information about these medicines. Selection of essential drugs is a continuing process taking into consideration the changing health priorities, epidemiological situation, progress in the pharmacological and pharmaceutical knowledge. The concept of essential medicines will help in the promotion of rational use of medicines in society.

Indian scenario - India is a developing country with limited resources. There is a significant burden of diseases in Indian population. Lot of resources of country get wasted in unnecessary diagnostic procedures and due to irrational use of medicines.

Important shortcoming of medical curriculum is that the teaching and training put more emphasis on diagnostic

Guidelines for Rational Drug Prescribing

First decide whether the drug is needed or not in the patient.



Select the group of drug to be prescribed on the basis of efficacy, safety, suitability and cost of therapy.



Select a drug from the group which is time tested and about which doctor has sufficient knowledge.



**Decide the dose in the patient.
Decide the route of administration.
Decide interdose interval.
Decide duration of therapy.**



**Monitor the efficacy and safety of drug.
If it is not emergency, then give sufficient time to drug to manifest its effect.
Do not change the drug on the basis of whims, fancy and material consideration.**



Avoid repeat prescription. Review the patient regularly.



**Give the information to the patient regarding the significance of drug therapy
in the illness, how to take the drug, how long to take, any precaution while taking the drug, how to store the drug and if any undesirable effect occurs what is to be done.**

rather than therapeutic aspects of diseases. Medical curriculum need to be modified in the interest of science and society. Medical curriculum must enable the undergraduates and post graduates to acquire knowledge and skills to manage common illnesses prevalent in country promptly and effectively through proficiency in clinical acumen and rational approach towards use of medicines.

Suggested reading.

1. Current medical diagnosis and treatment - 2015.
2. Conn's current therapy 2015.
3. Goodman & Gilman's Manual of Pharmacology and Therapeutics 2nd edition 2015.
4. Basic and Clinical Pharmacology Catzung 13th edition 2015.
5. Complete drug reference, Martindale 38th edition 2014.

If the drug is judiciously used, then it will offer hope of saving life, re-establishing the health and alleviating the suffering while injudicious use of drug causes more harm than benefit to the patient and exposes the prescriber to a risk.

“Medicines are nothing in themselves, but are the very hands of gods if employed with reason and prudence”

“Every prescription is the beginning of a new experiment Begin it carefully, remain vigilant make the patient healthy get blessed from the almighty.

