A Review on Fixed Dose Combinations: Irrational Drug Combinations and Patient Compliance.

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Abstract **- Medicines play an important role in healthcare delivery, and when used properly, can help cure diseases, relieve symptoms and alleviate patient suffering. Nonetheless, irrational use of medicines remain a major issue facing most health systems across the world.**

keywords **- Irrational drugs combinations, fixed dose combinations, Polypharmacy.**

1. INTRODUCTION:

The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product. When two or more drugs are combined in a fixed dose formulation like tablet, capsule, syrup, powder or injection, then their plasma half-life should approximately be same. The ratio of dose would depend on the volume of distribution and peak plasma concentration.

If the combination of drugs is illogical in terms of plasma half-life and pharmacokinetics of the drug, the combination should be termed as irrational drug combination. Large numbers of such irrational drug combinations are available in the market which unnecessarily increase the cost of medication and add to the side effects of the therapy [1].

The World health organization (WHO) estimates that more than half of all medicines are inappropriately prescribed, dispensed, or sold. Additionally, around 50% of patients fail to take their medicines correctly. The problem of drug combination use is known to be worse in developing countries with weak health systems, where mechanisms for routine monitoring of medicine use are often not well developed or are at times non-existent.

Tackling the issue of drug combination use is considered to be essential not only to improve healthcare delivery towards ensuring patient safety, but also to allow for optimal utilization of resources. This stems from the fact that as much as 25%–70% of overall health expenditure in developing countries is spent on medicines whereas, around 10% of health expenditure in most high-income countries is consumed by medicines [2].

In many developed countries, a well-functioning drug and therapeutics committee (DTC) has been shown to be very effective in addressing drug use problems. However, in many developing countries DTCs do not exist and in others they do not function optimally, often due to lack of local expertise or a lack of incentives [3].

Statistics suggest irrational use of medicines was listed among the top 10 causes of morbidity and mortality in the U.S. and it cost approximately US$870 million to provide care and treatment for those who were admitted to the hospital due to adverse medical events in the UK [4].

The most common problems associated with irrational use of medicines include selection of medicines without consideration for cost-effectiveness and efficacy, inefficient procurement of unnecessarily expensive drugs, failure to prescribe medicines in accordance with standard treatment protocols, poor dispensing practices resulting in medication errors, improper patients adherence to dosing schedules and treatment regimens, and inappropriate self-medication [5].

In addition, more than 50% of patients worldwide failed to take their medications properly. Either overuse or underuse of antibiotics can also result in serious antimicrobial resistance.

The overuse, underuse or misuse of medicines results in wastage of scarce resources and widespread health hazards [6].

Examples of irrational use of medicines include: use of too many medicines per patient ("poly-pharmacy"); inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections; over-use of injections when oral formulations would be more appropriate; failure to prescribe in accordance with clinical guidelines; inappropriate self-medication, often of prescription-only medicines; non-adherence to dosing regimens [7].

Uses of Fixed Dose Combinations (FDC's) are very prevalent in India by health professionals & physicians in order to provide quickly and better patient compliance. However, it has been found that in most of the cases of treatment, the sufferer or patient are being treated with FDC's that are not relevant to the disease with one or the other drug content of FDC's. Such treatment not only lead to financial burden on patient but also put him/her at the risk of toxicity, serious adverse effect, drug resistance and encourage risk of incompatibility and unethical practices.

From the literature study, it has been evident that developing countries like India is weakly regulated in terms of use of FDC's with irrational combination of drugs. The huge population sufferings, lack of awareness regarding healthcare and literacy especially in rural areas, poor healthcare system, costly and private healthcare facilities are being major concern.

Recently in 2016, Ministry of Health and Family Welfare Government of India through a gazette has banned 344 FDC's which are unethical and irrelevant in their contents and therapeutics use.
The ban follows through recommendations of an expert committee formed to examine the efficacy of these FDC's. In spite of the fact, such combinations (FDC's) are continue to prescribe and used in treatment making it necessary to think of regulations. Therefore, the objective of present study emphasizes the use of banned & irrelevant FDC's in current practices [8-10].

2. DISCUSSION: [11-12]

In the present study, literature survey and market survey was carried out at various physicians and pharmacists in local nearby areas of Nagpur. Around hundred prescriptions were evaluated for prescribed FDC's with respect to the contents and their relevance to the treatment. Some of the examples of such FDC's are described below:

2.1.1. Ampicillin and Cloxacillin:

Ampicillin is effective against Gram negative bacilli but Cloxacillin which is an Antistaphylococcal penicillin not effective against Gram negative bacilli. The Gram negative and Staphylococcal (Gram positive) mixed infection of both rarely coexists. Hence their combination would be useless along with the cost of therapy and bacterial resistance of the drug.

2.1.2. Antibacterial and Antiamoebic Combinations:

Ciprofloxacin and Metronidazole, Norfloxacin and Tinidazole and Ofloxacin and Ornidazole are such commonly available FDCs. In bacterial diarrhoea occurs then only anti-bacterial drug is effective and antiamoebic drug is useless and vice versa. Amoebiasis and bacterial diarrhoea rarely coexist and hence one drug of the combination would be effective and other is useless.

2.1.3. NSAIDs Combinations:

Nimesulide, diclofenec, ibuprofen and paracetamol are some non-steroidal anti-inflammatory drugs (NSAIDs). There is no need of combining one NSAID (nimesulide, diclofenec, and ibuprofen) with Paracetamol. Because they having identical pharmacological actions. Also there is an increased risk of hepatotoxicity and nephrotoxicity within NSAIDs combinations.

2.1.4. H_2 Blocker (Ranitidine) and Antispasmodic Drug (Dicyclomine):

Peptic ulcer is characterized by high level degree of gastric acid but not due to spasm of smooth muscles tissue and it will subside only by reducing acid in stomach by use of H_2 blocker (Ranitidine) or proton pump inhibitor drugs (Omeprazole, Pantoprazole or Lansoprazole). So there is no need of combining H_2 blocker (Ranitidine) with antispasmodic drug (Dicyclomine).

2.1.5. Antacid and Antianxiety Drug

The peptic acid disease is rarely associated with psychosomatic basis. So, there is no use of combining antianxiety drug like diazepam with antacids. Antacid also reduce the absorption of antianxiety drugs. Example: Dried Aluminium Hydroxide Gel + Prophantheline + Diazepam Brand Name: Ulsedin Tablet. Mfg.by: South India Research Institute Pvt. Ltd.

2.1.6. Mucolytic Agent and Antibacterial:

Ambroxol and Ciprofloxacin or Cefadroxil or Roxithromycin. Ambroxol is a mucolytic agent used to liquefy thick respiratory secretions. There is no need of combining the combination of mucolytic agent with antibacterial, as thick secretions in respiratory tract is not always due to respiratory infections.

2.1.7. Metformin and Glimepiride and Pioglitazone:

Metformin is used in obese type 2 diabetes mellitus and sulphonylureas (glimepiride) is indicated in non-obese type 2 diabetes mellitus. Accordingly other drug should be added only when monotherapy fails. Here metformin is to administer after meal and sulphonylurea (glimepiride) before meal therefore even both drugs required.it is better to taken or administer them separately. Pioglitazone used in case of insulin resistance. Hence there is no justification in combining these combinations.

2.1.8. Domperidone and Proton Pump Inhibitors:

Proton pump inhibitors (PPI) such as Omeprazole, Pantoprazole and Lansoprazole are used to reduce gastric acid secretion in peptic diseases and give symptomatic relief. The combination of PPI with antiemetic drug (Domperidone) is irrational or not useful because PPI is not always associated with vomiting.

2.1.9. Mebendazole and Pyrantel-pamoate or Levamisole:

The mebendazole dose is to be taken twice for three days whereas Pyrantel-pamoate or Levamisole is to be administered as a single dose. Hence there is mismatch in the dosages schedule of both drugs. So the combination of such two anthelminthic drugs is irrational.

2.1.10. Leukotrine Antagonist (Montelukast) and Bambuterol or Levocetirizine:

The leukotrine antagonist (montelukast) which is used for the management of moderate persistent asthma as an alternative to inhaled steroid. Levocetirizine is an antihistaminic drug which has limited role in the control of asthma as it is not only histamine that triggers the asthma attack. Bambuterol is a long acting beta-2 agonist which has role in the management of persistent and severe persistent asthma. Hence there is no justification in combining of Montelukast with Bambuterol or Levocetirizine.

3.2 Good Prescribing [12-13].

The term "good prescribing" is often used in literature, its meaning remains quite elusive. "The National Health Service (NHS) as a whole might define it as the lowest-cost prescribing that meets public health needs. The Department of Health and commissioners are keen to monitor prescribing and may measure good prescribing according to the available information and,

as this largely relates to drug costs, their definitions of good prescribing tend to use cost as the focus. The pharmaceutical industry may look on good prescribing as prescribing of the latest drug to all patients who have need of treatment on the basis that new equals better. Evidence-based practitioners tend to define it as the use of therapies proven to be most effective in randomised controlled trials (RCTs), or according to evidence-based guidelines".
According to Aronson, a good prescribing is one that "recommends a medicine appropriate to the patient's condition and minimizes the risk of undue harm from it". Aronson's definition is in accordance with Barber, who explained that a good prescribing is one that achieves the four aims, namely.
(1) To maximize effectiveness
(2) Minimize risks
(3) Minimize costs
(4) Respect the patient's choices.

3.3. Irrational Prescribing [14].
Irrational prescribing refers to prescribing that fails to conform to good standards of treatment
This may manifest in five different ways, namely:
1. Under-prescribing
2. Over-prescribing
3. Incorrect prescribing
4. Extravagant prescribing
5. Multiple prescribing

3.3.1. Under-prescribing- Under-prescribing indicates the instance where the medicines required are not prescribed, or an insufficient dosage or treatment duration is issued. This can occur when, for instance, an inadequate weight-based dose is administered in patients such as children.
3.3.2. Over-prescribing- Over-prescribing refers to instances where a medicine that is not indicated is prescribed, or if indicated, the duration of treatment is too long or the quantity of medicine given to patients exceeds the amount required for the current course of therapy. This can include, for instance, giving 21 days course of an antibiotic for a minor infection that requires just 7 days of treatment, or when an antibiotic is prescribed in the first place for a suspected viral infection.
3.3.3. Incorrect prescribing- Incorrect prescribing also occurs when a medicine is given for the wrong diagnosis, the prescription is prepared improperly, or adjustments are not made to incorporate the patient's co-existing medical, genetic, or environmental conditions. An example is when a doctor fails to consider an allergy that a patient may have which could be triggered by a new medication being prescribed.
3.3.4. Extravagant prescribing- Extravagant prescribing is said to have occurred when a prescriber issues a more expensive medicine when a less expensive one of comparable safety and efficacy exists, or where a prescriber treats a patient symptomatically instead of tackling the underlying serious condition. An example may include writing an unnecessarily expensive cough mixture when it presents no documented extra benefits from commonly available cheaper options.
3.3.5. Multiple prescribing- Multiple prescribing is also deemed to have taken place when two or more medicines are prescribed when fewer would have achieved same effect, or where prescribers treat several related conditions when treatment of the underlying (primary) disorder would improve or cure the other conditions.

3.4. Factors contributing to irrational use of medicines [15].
There are many factors that contribute to the irrational prescribing or use of medicines. These factors can be traced to various stages of the medicine use cycle, and can be broadly categorized into:-
1. Those emanating from patients
2 .Prescribers
3. Workplace (health system)
4. Supply system (including industry influences)
5. Regulation
6. Drug information or misinformation
7. Or combination of these factors.

3.4.1. Patients- Uninformed patients who may have the perception that there exists a pill for every ailment can exert undue pressure on health providers to prescribe medicines, even when this is not needed. Macfarlane et al. for instance, investigated the impact of patients' pressure on antibiotic prescribing in the management of acute lower respiratory tract illness at 76 primary care facilities in the UK. Their results indicated that, of the patients evaluated, 74% were prescribed antibiotics, and that non-clinical factors influenced prescribing 44% of those receiving antibiotics, of which patient pressure was the reason in more than half.
3.4.2. Prescribers- Regarding prescriber-related factors, irrational prescribing can arise as a result of several internal or external factors. For instance, the prescriber may lack adequate training, or there may be inadequate continuing education, resulting in the reliance on out-dated prescribing practices which may have been learnt while under training**.**
3.4.3. Workplace- Workplace issues, such as lack of laboratory facilities typical of many resource-poor settings may promote inappropriate prescribing. For instance, a prescriber may want to conduct laboratory investigation to confirm the presence of infection, but may have to resort to empirical treatment if laboratory facilities are unavailable.

3.4.4. Supply System- Other issues, such as under-staffing, medicine shortages, and a lack of an inventory of a list of medicines from which choices need to be made are some of the factors known to promote irrational prescribing in many developing countries. There are also practices by pharmaceutical companies that are seen to enhance irrational prescribing.
3.4.5. Regulations- Pharmaceutical sales representative visits to doctors have been found to not only increase the prescription of the promoted drug, but also to lead to a decrease in the market share of competitor products.
3.4.6. Drug Information or Misinformation- Pharmaceutical sales representatives often exaggerate the efficacy of their products while questioning the integrity of competitor brands, and may even encourage off-label use. Over-reliance on such sources of information could lead to irrational prescribing.

3.5. Impact of the irrational use of medicines [16-17].

The impact of irrational medicines use can vary widely. Firstly, when medicines are used inappropriately, the risks of adverse drug reactions (ADRs) is increased, especially in geriatric patients or in co-morbid individuals who may have compromised physiologic functions.
Irrational prescribing can also expose patients to the possibility of developing drug dependence to certain medicines, such as pain killers and tranquillizers.
Inappropriate prescribing practices such as the overuse of injections can expose patients to the contraction of certain injection-related conditions, such as abscesses, hepatitis B, and HIV/AIDS. Indiscriminate prescribing of injections can also increase workload, as health professionals need to administer doses.
When medicines are prescribed indiscriminately, it may also exert a psychological effect on patients who may come to the conclusion that there exists "a pill for every ill", thereby causing a cycle of excessive demand for medicines.
In addition, the inappropriate use of medicines can lead to wastage of scarce health resources, which can further reduce the availability of other vital medicines or increase treatment cost. The WHO estimates that the appropriate use of medicines can result in about 50%–70% cost-efficiency in medicines expenditure.

3.6. Strategies to Tackle Irrational Prescribing [18].

According to the WHO, irrational prescribing is a "disease" which is difficult to treat prevention is however possible.
There exist various strategies to change patients' and prescribers' behaviour toward she promotion of rational prescribing. These strategies can be grouped broadly as targeted or system-oriented approaches.
Targeted approaches comprise educational and managerial interventions, System-oriented strategies include regulatory and economic interventions.
Educational interventions are often aimed at persuading or informing, and this usually involves the use of printed materials, seminars, or face-to-face contacts. However, educational interventions may influence prescriber knowledge and awareness, but their effectiveness in changing behaviour remains modest unless used in combination with other strategies.
Managerial strategies, on the other hand, are mainly aimed at guiding practice. Such managerial interventions that may be employed include monitoring, supervision and feedback, the use of a restrictive medicines list, drug utilization reviews, or the use of structured prescription forms.
Economic strategies, on the other hand, are aimed at promoting positive financial incentives while at the same time eliminating perverse incentives for prescribers.
Regulatory interventions utilize laws and regulations to influence prescribers' practices through restrictions and requirements. An example of such an approach includes allocating each medicine a minimum level of prescriber or health facility.

4. CONCLUSION [19-20].

In the present project attempts have been made to focus need of rational use of medicines particularly FDC's by healthcare practitioners. There are several examples studied for unethical practice with respect to relevance of treatment, duration, cost and safety of patient were compromised.

1. WHO advocates 12 key interventions to promote more rational use.
2. Establishment of a multidisciplinary national body to coordinate policies on medicine use.
3. Use of clinical guidelines.
4. Development and use of national essential medicines list.
5. Establishment of drug and therapeutics committees in districts and hospitals.
6. Inclusion of problem-based pharmacotherapy training in undergraduate curricula.
7. Continuing in-service medical education as a licensure requirement.
8. Supervision, audit and feedback.
9. Use of independent information on medicines.
10. Public education about medicines.
11. Avoidance of perverse financial incentives.
12. Use of appropriate and enforced regulation.
13. Sufficient government expenditure to ensure availability of medicines and staff.

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