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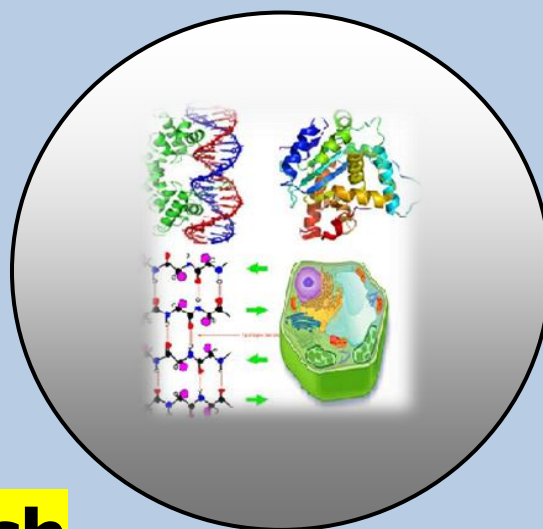
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Prescribing Trends of Fixed Dose Combination Using WHO Guidelines in a Tertiary Care Teaching Hospital of Lucknow District**Ahmad Najmi, *D.K. Niranjana, **Umme Aiman and ***M.M. Khan**

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ABSTRACT

Fixed dose combinations (FDCs) are a combination product of two or more drugs in a single dosage form. The objective of the study is to evaluate the prescribing pattern of FDCs in a tertiary care hospital of north India, using WHO guidelines. It was a prospective observational study. Study was conducted in the outpatient departments (OPD) of medicine, surgery, obstetrics & gynecology, ENT, ophthalmology, orthopedics & skin. All prescriptions over a period of 30 days in each OPD were analyzed. FDCs prescribed were recorded and evaluated for rationality, using WHO guidelines. FDCs from the causality, wards, ICU, TB & Chest department & HIV unit were excluded. Maximum FDCs were prescribed in medicine (29.51%), followed by ENT (18.62%) and surgery (15.81%). Minimum FDCs were prescribed in the department of ophthalmology (4.86%). Out of 209 FDCs, only 30 % were rational and 60.5 % were irrational. 80 % of the prescribers were unaware regarding the active pharmacological ingredient of FDCs. From the total prescriptions analyzed, FDCs of the antimicrobial agents were found to be maximum. There were no banned FDCs prescribed in our study. 90 % of FDCs were prescribed by brand names & only 10 % of FDCs were prescribed by generic names. . Approximately five percent of FDCs were costing more than Rs. 500. In 70 % of FDCs, the individual component was cheap but the combination increased the cost. The study showed the trend towards prescribing irrational FDCs. Prescriber should be critical about FDCs. Guidelines for manufacturing and sales of FDCs should be followed.

Key Words: Rational, WHO guidelines, Irrational, Fixed dose combination (FDCs).

INTRODUCTION

Fixed dose combinations (FDCs) are a combination product of two or more drugs in a single dosage form. Only some of the FDCs are rational and justified. Many of the FDCs are

vigorously promoted by pharmaceutical companies for their own benefits. The latest WHO essential medical list incorporates only 23 FDCs. To be combined two drugs should have approximately equal half-life, apparent volume of distribution & peak plasma concentration. Various advantages of fixed Drug combination (FDCs) are better efficacy, reduced adverse drug reactions, better compliance & reduced pill burden, delay development of drug resistance & broader spectrum of antibacterial activity. Various disadvantages of FDCs are emergence of resistance, increase in cost of therapy, difficulty in dose adjustment & difficulty in adverse drug reaction (ADR) assessment. Irrational use of FDCs is a menace worldwide. The concept of rational FDCs is still in the embryonic phase in India. The market is flooded with large number of irrational FDCs. So the aim of our study is to evaluate the prescribing pattern of rational & irrational FDCs in a tertiary care teaching hospital of North India.

MATERIAL AND METHODS

It was a prospective observational study. This study was approved by institutional ethical committee. It was carried out between August 2014 to January 2015 in a tertiary care teaching hospital of north India, Career Institute of Medical Sciences, Lucknow, UP. Study was conducted in the outpatient department (OPD) of medicine, surgery, obstetrics & gynecology, ENT, ophthalmology, orthopedics and skin. All prescriptions over a period of 30 days in each OPD were analyzed. FDCs prescribed were recorded and evaluated for rationality. A total of 690 prescriptions were analyzed. These 690 prescriptions contained 451 FDCs meant for oral use only. By excluding the repetitions, the total numbers of FDCs from the entire department were 268. These 268 FDCs included interdepartmental repetitions, thus by excluding them the total numbers of FDCs were 209, which were considered as n for analysis. These FDCs were analyzed for rationality using WHO guidelines. The following guidelines¹⁰ were followed.

According to WHO guidelines, FDCs are rational when they fulfill following criteria:

1. Active pharmacological ingredients (API) with complementary mechanism of action
2. Decrease in the occurrence of resistance for antimicrobial agents
3. Increase in the efficacy of combinations
4. Decrease in the incidence of ADR or toxicity
5. Increase in the compliance of drug therapy with decrease pill burden
6. Decrease in the total cost of therapy
7. Dose of each API should be appropriate for defining / larger group of population

The FDCs was termed as absurd if it shows

1. No justification for combination
2. No increase in efficacy than individual drugs

The FDCs in our study were classified into four categories as rational, irrational, absurd & banned⁶. Inclusion criteria were prescriptions from the outpatient department. FDCs from the causality, wards, ICU, TB & Chest department as well as HIV unit were excluded.

RESULTS

The percentage of FDCs prescribed in different departments has been shown in Figure 1. Maximum FDCs were prescribed in medicine (29.51%), followed by ENT (18.62%) and then surgery (15.81%). Minimum FDCs were prescribed in the department of ophthalmology (4.86%). Categorization of FDCs according to WHO guidelines for rationality is depicted in figure 2. Out of 209 FDCs, only 30 % were rational and 60.5 % were irrational.

The comparison of the FDCs prescribed by brand names and generic name is shown in figure 3. The majority of the FDCs (90%) were prescribed by the brand names. The knowledge of the prescriber about the API of the prescribed FDCs is given in figure 4. Prescribers were questioned about the contents of the prescribed FDCs which were prescribed as brand names. It was found that they were unaware of the contents of 80 % of the FDCs. The pharmacological classes of the FDCs prescribed with categorization as per WHO guidelines are shown in table 1. From the total prescriptions analyzed, FDCs of the antimicrobial agents were found to be maximum i.e. 60 in number out of which 18 were rational. There were no banned FDCs prescribed in our study.

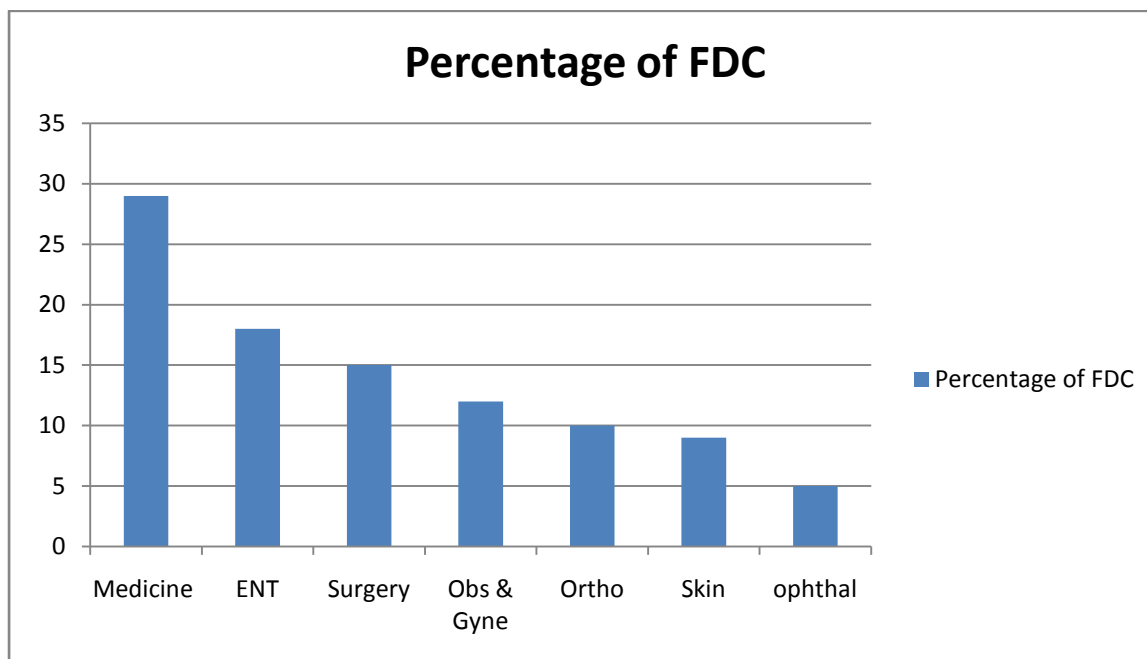


Figure 1. Total percentage of fixed dose combinations (FDCs) prescribed in different departments.

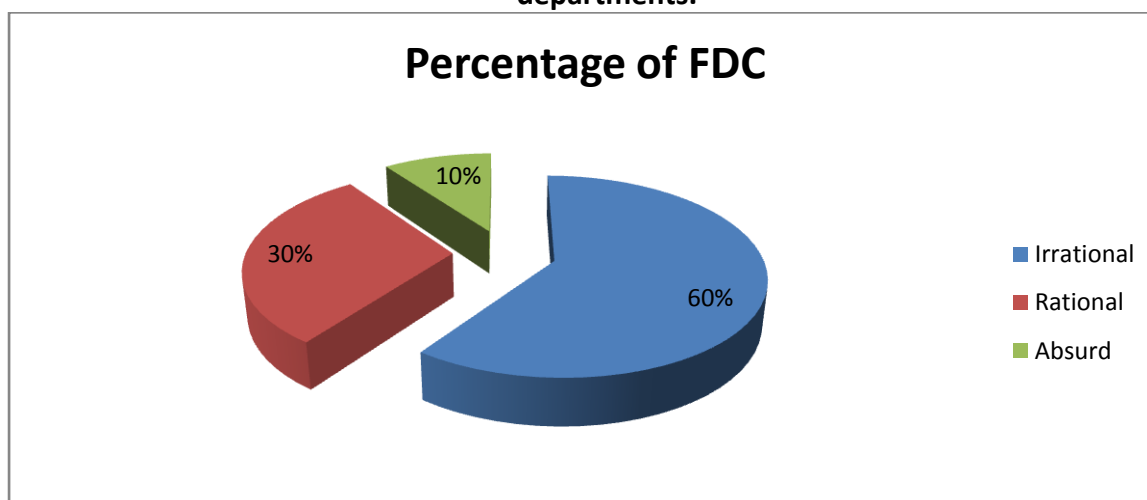


Figure 2. Categorization of the FDCs based on WHO criteria for rationality. Values are expressed as percentages.

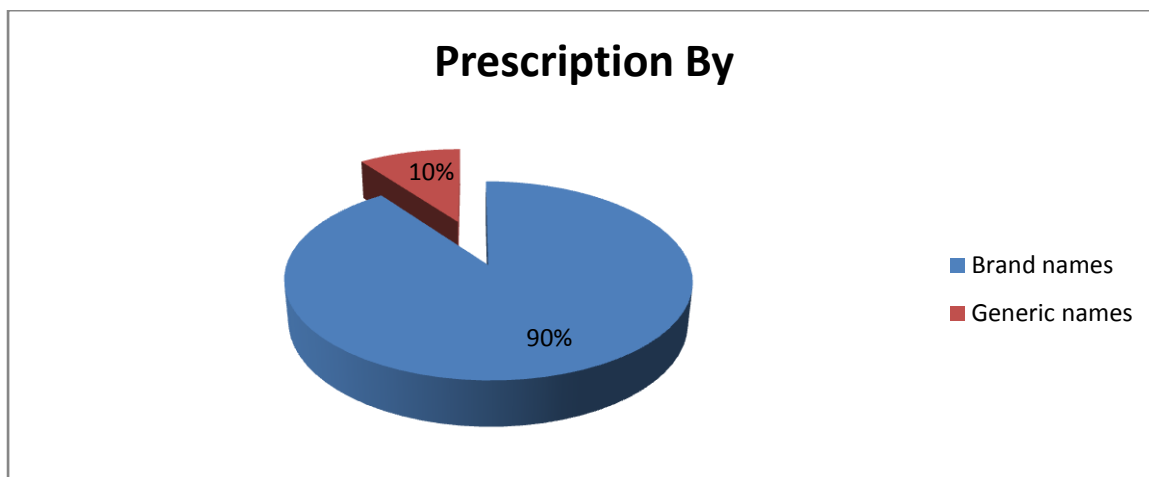


Figure 3.FDCs prescribed by brand names and generic names.

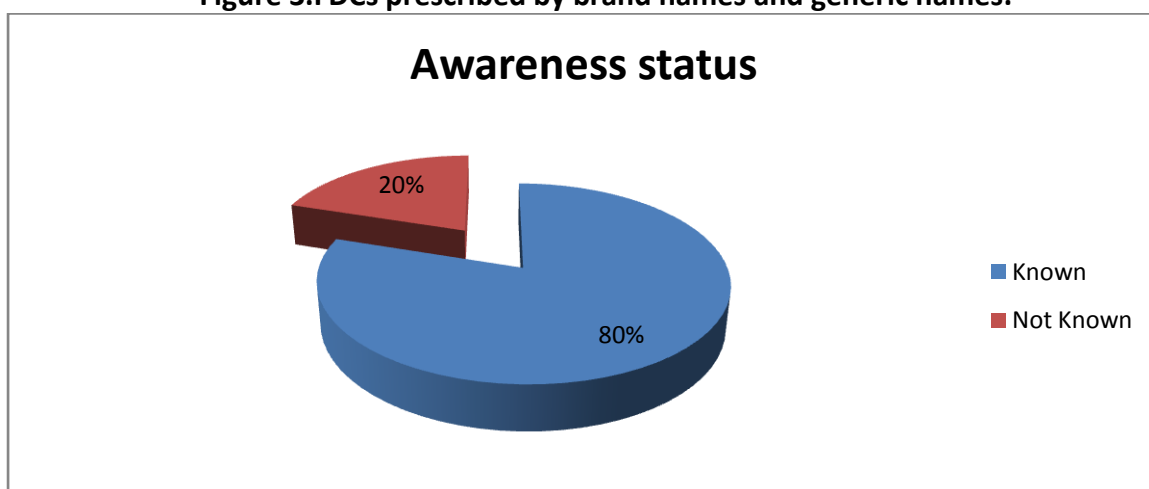


Figure 4. Prescribers awareness about API.

Table 1. Pharmacological Classes of FDCs prescribed with categorization as per WHO guidelines.

Classes of FDC	n	Rational	Irrational	Absurd
Antimicrobials	60	18	38	04
Antiinflammatory drugs	56	24	30	02
Cough and Cold agents	22	06	14	02
Nutritional supplements	18	05	12	01
Antiulcers	17	06	10	01
Antihypertensives	15	07	08	0
Hypolipidemics	11	05	06	0
Antidiabetics	11	04	07	0
Antihistaminics	09	0	08	01
Digestive enzymes	06	0	06	0

DISCUSSION

The study evaluated the prescription pattern of FDCs in a tertiary care teaching hospital. The study showed the trend towards prescribing irrational FDCs. The positive aspects of the study were not using the banned drugs in the hospital. There are also some limitations regarding small sample size, lack of indoor prescriptions & lack of enrollment of causality, TB chest, HIV and ICU patients. Approximately 30 % of FDCs were rational as they fulfilled all the WHO criteria. The most common examples were amoxicillin plus clavulanic acid, artemether plus lumefantrine, trimethoprim plus sulfamethoxazole.

Some of the irrational combinations are discussed herewith. The combination of antiamoebic plus antibacterial is not recommended. Dysentery may be amoebic or bacillary. Mixed infection is very rare. So there is no justification in combining antiamoebic drugs with antibacterial drugs. The combination will increase the cost as well as chances of drug resistance.

Next example is mucolytic agent plus antibacterial. Mucolytic drugs are used to liquify thick secretions in the respiratory tract. But thick secretions are not always due to infections. So there is no justification for combining antibiotics with mucolytic agent.

Next example is antitussive plus expectorant plus mucolytic plus decongestants. Antitussives are used to suppress dry irritating cough. Expectorants are used in productive cough. So both the drugs have an opposite action. So there is no justification in combining antitussive drugs with expectorants.

The combination of NSAIDs plus serratiopeptidase is not recommended. Serratiopeptidase are oral proteolytic drugs. These are claimed to be anti-inflammatory effects. Being protein in nature, they are destroyed in the GIT, so it is difficult for them to reach at the site of action in an active form. Also they are costly drugs. So there is no justification in combining NSAIDs with serratiopeptidase.

In this study, there were 90 % FDCs which were outside the list of FDCs in the WHO essential medical list (EML) and national list of essential medicine (NLEM) and were not according to WHO criteria towards rational FDCs. Sixty one percent FDCs were either pharmacologically incompatible or their pharmacokinetic parameter did not match or their API interacted with each other or the combination produce increase in adverse effects. They did not fulfill the WHO criteria for rationality. Ninety percent of FDCs were prescribed by the brand names and only 10 % of FDCs were prescribed by generic names. Few of the FDCs, prescribed by generic names were combination of amoxicillin and clavulanic acid, paracetamol and diclofenac.

Eighty percent of physician obtained information about these FDCs through drug detailers, 15 % through colleagues, 15 % through seniors and only 5 % searched the information on FDCs through authentic literature like books, scientific journals and authentic websites. This finding is in concurrence with previous findings suggesting that common sources of information about FDCs were medical representatives, colleagues, peers, monthly index of medical specialties (MIMS), current index of medical specialties (CIMS) and continuous medical education programs (CME)⁴. Approximately five percent of FDCs were costing more than Rs. 500. In 70 % of FDC, the individual component was cheap but the combination or the addition of second content increased the cost. FDCs are cost effective only when they are used for certain chronic diseases like tuberculosis, HIV & leprosy. For rest of the indications, the addition of second content almost always causes increase in cost.

This finding is parallel with the study supporting that there was marginal increase in the cost when FDCs were used instead of free drug components. Prescribing more than one drug leads to drug interactions and adverse drug reactions, which sometimes may be dangerous and life threatening needing hospitalization, increasing financial burden and reduction in quality of life. FDCs use is justified in conditions such as tuberculosis, malaria, HIV, leprosy and other chronic conditions as they increase the adherence to therapy. More than one third of new drugs added to the therapeutic armamentarium are FDCs. Some are very popular. Such FDCs do not find mention in standard text books, but the manufactures rip the benefit of huge sale and hence promote them vigorously by influencing prescribers' unethically. Indian government issues notification from time to time banning these irrational FDCs prohibiting their manufacture and sale. Till date 79 formulations have been banned. According to drugs and cosmetic act, 1940, FDCs are considered as new drugs and finished products needing proper evidence on their efficacy and safety. Hence randomized controlled trials may be necessary showing superiority over reference treatment. Drug regulatory bodies should take strict action against irrational FDCs. New FDCs require clearance from Drug Controller General of India (DCGI) and State Drug Controllers. However they are mostly marketed after the approval of state drug controller only.

CONCLUSION

Prescriber should be critical about FDCs. Guidelines for manufacturing and sales of FDCs should be followed. Some FDCs could be rational, provided it fulfills the WHO guidelines. There is a need of awareness of rational and irrational FDCs among prescribers. Government should make strict rules & regulation to prohibit the manufacturing & sales of irrational FDCs

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