Research Article

Evaluation of rationality of fixed-dose combinations prescribed in psychiatric patients

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Abstract

Background: There is a growing concern about the increasing number of irrational fixed-dose combinations (FDCs), which impose unnecessary financial burden, increase the occurrence of adverse drug reactions, and ultimately reduce the quality of life. **Aims and Objective:** To study the prescribing frequency of FDCs and to evaluate the rationality of FDCs prescribed in psychiatric patients. **Materials and Methods:** This prospective study was carried out in Pharmacology and Psychiatry Department of a tertiary care teaching hospital in Rajasthan, India. The data were collected in a case record form from patients of all ages and from either sex, who visited the outpatient department of psychiatry. Data were analyzed with the help of well-known comprehensive seven-point criteria by Panda et al, which were developed by carefully studying the guidelines of the World Health Organization and Committee for Proprietary Medicinal Products, Europe. **Result:** Total 383 drug formulations were prescribed in 200 patients of which 107 (27.93%) were in the form of FDCs. Most frequently prescribed FDC was escitalopram + clonazepam (22.44%), followed by amitriptyline + chlordiazepoxide (13.08%). The maximum score for the seven-point criteria for assessing the rationality of FDCs was 14, with each criterion carrying a score of 2. Scores obtained in this study ranged between 5 and 14 with an average of 8.79. **Conclusion:** Most of the FDCs were irrational according to the criteria used and only 28.57% of the FDCs were found to be rational considering safety and efficacy as the most important criteria for rationality. So, drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs.

KEY WORDS: Rationality; Irrational; Fixed-Dose Combinations; Drug Regulatory Bodies

Introduction

Fixed-dose combination (FDC) is a combination product of two or more active pharmacological ingredients (APIs) in a single dosage form. The FDC is an innovative product, its main advantages being increase in patient's compliance, decrease in pill burden, and reduced complications and cost.[1] Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period and at the lowest cost to them and their community.[2] There is a growing concern about the increasing number of irrational FDCs in the developing countries, which impose unnecessary financial burden; increase the occurrence of adverse drug reactions, including allergy, hospitalization; and ultimately reducing the quality of life.[3] Combining two or more drugs in a single formulation causes changes in its efficacy, safety, and bioavailability profile; hence, FDCs are treated as new drugs.[4] More than one-third of all the new drug products introduced worldwide during the last decade were FDC preparations. There are unfortunately no worldwide acceptable criteria to define irrational FDCs and no uniform principles or international standards for their development and regulatory

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assessment. The Indian laws are also not properly defined to grant marketing approval by central or state drug controlling authorities; hence, there is an increase in the number of irrational FDCs in the Indian drug market at an alarming rate.

There are various irrational FDCs related to psychiatric medicines such as alprazolam with imipramine, melatonin, sertraline, and fluoxetine, common in Indian market and rationality of many of these FDCs are still not reported.[5] We could not find any study related to evaluating the rationality of FDCs in Psychiatry Department and no such study was carried out at our institute; hence, this study was undertaken to study the prescribing frequency of FDCs and to evaluate the rationality of FDCs prescribed in psychiatric patients.

Materials and Methods

This prospective study was carried out in the department of pharmacology and psychiatry of a tertiary care teaching hospital in Rajasthan, India. After taking written informed consent from the patients or the patients' relatives, data were collected from the case papers of those patients. The data were collected from the patients of all ages and from either sex, who visited the outpatient department (OPD) of psychiatry. All cases with drug prescriptions were included during the study period and the patients not willing to give the information were excluded from the study. Approval from the institutional ethics committee was taken before starting the study. The data were collected in a case record form that includes patient's demographic details, OPD registration number, provisional diagnosis or diagnosis, chief complaints, and complete prescription.

Data were analyzed for the prescribing frequency of FDCs. All the FDCs were evaluated for its rationality with the help of a comprehensive seven-point criterion by Panda et al.,[6] which was developed by carefully studying the guidelines of the World Health Organization (WHO) (draft guidelines for the registration of FDC medicinal products) and Committee for Proprietary Medicinal Products, Europe (note for guidance on FDC medicinal products). These are well-known guidelines, which serve as a benchmark toward a rational FDC.[6] These criteria include all the dimensions of defining a rational FDC, and appropriate weighting (score) has been attached to each criterion. The maximum scoring of the seven-point criteria was 14 with each criterion carrying a score of 2. The total score thus obtained by a FDC will reflect its standing on the scale; however, it is to be noted that this score should not be viewed in isolation.

Seven-point criteria for evaluating the rationality of FDCs are as follows:

- The first point is that each API of the combination should preferably be in the "essential medicines list (EML)" of the WHO or in the National List of Essential Medicines (NLEM) of India.
- The dose of each API should meet the requirements for a defined population group. The dose and the proportion of each API present in FDC should be appropriate for the intended use.
- The combination should have the advantage of established evidence of efficacy and safety.
- The overall cost of the combination should preferably be less than the cost of the individual components.
- The FDC should facilitate either the reduction of the dose of individual drugs or their adverse effects.
- The pharmacokinetic (PK) parameters of each API should not be affected. There should be no unfavorable PK interaction between the APIs. In case of the PK parameters being different, the clinical benefits should be taken into consideration.
- Finally, the individual drugs should have different mechanism of action.

The WHO model list of the EML[7] and the NLEM[8] was used for the assessment of the first criteria. The dose of the individual APIs was verified from standard textbooks and *Martindale Extra Pharmacopoeia*. The published data regarding clinical evidence of safety and efficacy were collected from databases such as PubMed, Medscape, and the Cochrane library. The data on the reduction in dose and adverse effects were collected from the same databases. The cost data of individual components, as well as the FDCs, were obtained from the Indian Drug Review, Jan 2014 and ref Rx (ref Rx is a drug information/ reference book published monthly basis just like CIMS, IDR (Indian Drug Review)), July–October 2013. The detailed information about PK parameters was collected from standard textbooks and *Martindale Extra Pharmacopoeia*. The assessment of rationality was performed by adding score of each criterion for individual FDC.

All the data collected were analyzed using appropriate statistical tests.

Result

A total of 200 patients were included during the study period of 2 months and they were analyzed. Age of the patients ranged from 10 to 76 years with a mean of 38.14 years. Their major diagnosis included depression, schizophrenia, bipolar disorders, and so on, for which the drugs were prescribed.

A total of 383 drug formulations were prescribed to these patients with a mean of 1.92 drugs per patient. Among these, 107 formulations (27.93%) were prescribed as FDCs. There were total 14 different FDCs related to psychiatric disease. Most frequently prescribed FDC was escitalopram + clonazepam (22.44%), followed by amitriptyline + chlordiazepoxide (13.08%) (Table 1).

The results of the evaluation indicated that both the individual components were present in the EML of the WHO and NLEM of India in two (14.29%) of FDCs. In case of seven (50%) FDCs, at least one component was present in either the EML of the WHO or NLEM of India or both. In five (35.71%) FDCs, both the components were absent in both the EML of the WHO and NLEM of India. The dose and proportion of each API present in FDCs (100%) were found to be appropriate for the individual use. Among the FDCs, four (28.57%) combinations possess the advantage of efficacy and safety over individual

Table 1: Most frequently prescribed FDCs in psychiatry department

FDC	No.	%
Escitalopram + clonazepam	24	22.44
Amitriptyline + chlordiazepoxide	14	13.08
Risperidone + trihexyphenidyl	13	12.14
Pregabaline + methylcobalamin	11	10.28
Chlorpromazine + trihexyphenidyl	8	7.47
Escitalopram + etizolam	8	7.47
Olanzapine + fluoxetine	6	5.60

FDC, fixed-dose combination.

drugs administered separately based on established evidences. There was no established evidence in terms of therapeutic efficacy and safety for the remaining combinations. Most of the FDCs, that is, 13 (92.86%) were cost-effective when compared with their individual components except propranolol + flunarizine, which was expensive than the individual components. Figure 1 illustrates the difference in the cost of individual drugs and their combinations for the commonly prescribed brand names. Four (28.57%) FDCs provide published literature on the reduction of either dose of individual drugs or their adverse effects. A total of 50% of combinations were found to have similar PK profile and all the combinations (100%) were having different mechanism of action.

The maximum score on the seven-point criteria for assessing the rationality of FDCs was 14, with each criterion carrying a score of 2. Scores obtained in this study ranged between 5 and 14 with an average of 8.79. Six FDCs scored 7, four FDCs scored 8 to 11, and four FDCs scored 12 to 14. The scoring obtained by each FDC in this study is shown in Table 2, and Figure 2 shows the score distribution for the FDCs prescribed in this study.

Discussion

In our study, 27.93% formulations were prescribed as FDCs. Similar results were also found in other studies in which 22.5% of the prescriptions contained psychotropic FDCs.[9] Another study related to psychiatry showed that not a single FDC was prescribed by the doctors to make their prescription more rational.[10]

Most frequently prescribed FDC was escitalopram + clonazepam followed by amitriptyline + chlordiazepoxide. In one study, olanzapine + fluoxetine followed by escitalopram + clonazepam was found to be the most commonly prescribed combination for depression.[11] In another study, trifluoperazine + trihexyphenidyl was found to be the most commonly prescribed FDC for schizophrenia because this combination was available in hospital pharmacy free of cost.[9]

The results of evaluation indicated that both the individual components were present in the EML of the WHO and NLEM of India for two (14.29%) of the FDCs. In 50% of FDCs, at least one component was present in either the EML of the WHO or NLEM of India or both. A similar study was conducted in Cardiovascular Department in which 11.1% of the FDCs were present in either the EML of the WHO or NLEM of India whereas for 66.6% of the FDCs at least one component was present in either the EML of the WHO or NLEM of India.[12] Another similar study on

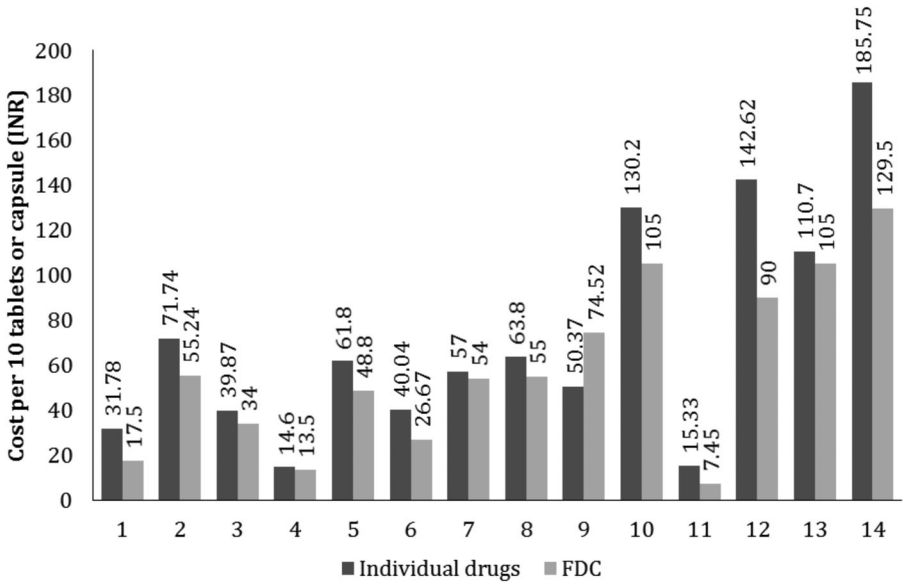

Figure 1: Comparative costs of individual drugs and their FDCs (1, amitriptyline + chlordiazepoxide; 2, escitalopram + clonazepam; 3, etizolam + propranolol: 4, chlorpromazine + trihexyphenidyl; 5, olanzapine + fluoxetine; 6, clonazepam + propranolol; 7, risperidone + trihexyphenidyl; 8, escitalopram + etizolam; 9, propranolol + flunarizine; 10, paroxetine + clonazepam; 11, trifluoperazine + trihexyphenidyl; 12, donepezil + memantine; 13, desvenlafaxine + clonazepam; 14, pregabalin + methylcobalamin; FDCs, fixed-dose combinations.).

Table 2: Total score of individual FDC

FDC	Total score
Amitryptaline + chlordiazepoxide	9
Escitalopram + clonazepam	8
Etizolam + propranolol	9
Chlorpromazine + trihexyphenidyl	8
Olanzapine + fluoxetine	14
Clonazepam + propranolol	7
Risperidone + trihexyphenidyl	7
Escitalopram + etizolam	6
Propranolol + flunarizine	5
Paroxetine + clonazepam	12
Trifluoperazine + trihexyphenidyl	7
Donepezil + memantine	12
Desvenlafaxine + clonazepam	6
Pregabalin + methylcobalamin	13

FDC, fixed-dose combination.

antihypertensive drugs showed that about 40% of the FDCs were present in either the EML of the WHO or NLEM of India whereas for 50% of FDCs at least one component was present in either the EML of the WHO or NLEM of India.[6] One more study has also shown that 20% of the FDCs were in the EML of the WHO and 10.2% of the FDCs contained only single component as a part of the EML of the WHO.[5] All these studies have shown that percentage of drugs from the EML of the WHO and NLEM of India is less. Inclusion of drugs from the EML of the WHO and NLEM of India should be more while manufacturing FDCs to promote rational use of medicines because these drugs are having established safety and efficacy profile.[8]

The dose and proportion of each API present in the FDCs (100%) were found to be appropriate for the individual use.

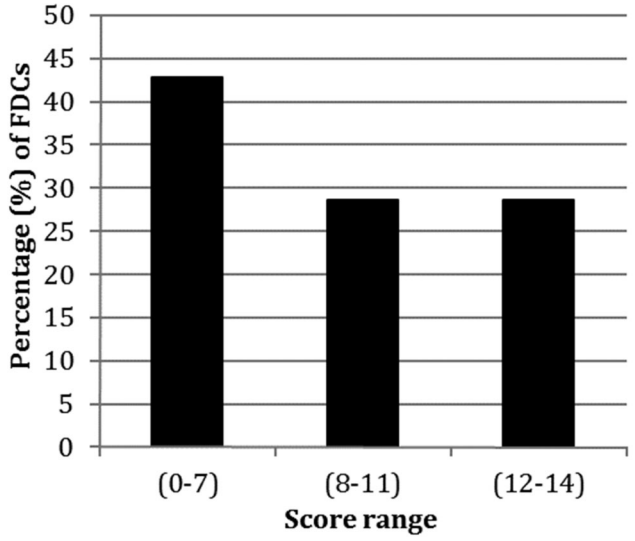

Figure 2: Score distribution of FDCs.

Similar results were also obtained in other studies that were conducted for rationality.[6,12]

After literature search, only four combinations (olanzapine + fluoxetine, clonazepam + paroxetine, donepezil + memantine, and pregabalin + methylcobalamin) were found to have the advantage of efficacy and safety over individual drugs administered separately.[13–17] In published literatures, these FDCs have also shown the reduction of either dose of individual drugs or their adverse effects. There was no established evidence in terms of therapeutic efficacy and safety for the remaining combinations. A combination of escitazolam + clonazepam has been approved by the DGCI Drug Controller General of India.[18] However, we could not find any data on its safety and efficacy. Evidence of safety and efficacy is of utmost importance when the two drugs are combined together as a single formulation.[6] Similar studies in Cardiovascular Department and for antihypertensive drugs have shown established safety and efficacy in 88% and 75% of the combinations.[12] Safety and efficacy is one of the important criteria for rationality of the FDCs, and those studies were found to have more FDCs with established safety and efficacy. So, those studies were having more rational combinations as compared to our study.

Most of the FDCs were cost-effective when compared with their individual components except propranolol + flunarizine, which was more costly than the individual components. Other studies have also shown similar results. Rational therapy calls for the prescription of less costly single ingredient drugs more often than the costlier combinations. Hence, FDCs are commonly used because of their cost-effectiveness.[19]

Half of the combinations were found to have similar PK profile. In this study, mainly plasma half-life was taken for PK profile except for one combination (pregabalin + methylcobalamin) for which clinical benefit was taken into consideration because methylcobalamin (vitamin B_{12}) is stored in our body.[8] All the combinations were having different mechanism of action, which is good for rationality. But in this study, all criteria were used together to establish rationality.

Unfortunately, many FDCs being introduced in India are usually irrational. Popularity of FDCs is increasing rapidly if more than one disease is present in patients. In Psychiatry Department also, many FDCs are prescribed for the same reason. Average low scoring of FDCs in this study was due to the lack of evidence for the efficacy and safety in many FDCs. So, overall FDCs prescribed in psychiatry department were found to be irrational according to the criteria used. Only 28.57% of the FDCs were found to be rational as they fulfilled most of the criteria considering safety and efficacy as the most important criteria for rationality. Using published articles as reference, it was found that most of the FDCs were cost-effective but many of them were lacking safety and efficacy. More trials need to be conducted for the safety and efficacy of those combinations. Irrational FDCs unnecessarily add cost, adverse effects, and resistance in case of antimicrobial agents. Hence, rational FDCs should be encouraged and drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs. Standard criteria should be formed with the help of regulatory bodies, health-care professionals, researchers, and pharmaceutical companies for evaluating the rationality of

the FDCs on an individual basis. More studies need to be conducted to evaluate rationality of the FDCs present in India by using these standard criteria.

Conclusion

Most of the FDCs were irrational according to the criteria used and only 28.57% of the FDCs were found to be rational considering safety and efficacy as the most important criteria for rationality. So, drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs.

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