Physician’s knowledge, attitude and practice of fixed drug combinations: Can we recognize the lacunae?

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Abstract

Objective: The Indian pharmaceutical market is flooded with different fixed drug combinations (FDCs), many of which lack a rational justification. The study aimed to assess the knowledge, attitude, and practice (KAP) regarding FDCs among the physicians of a tertiary-care teaching center. Method: The target sample size for this cross-sectional study was calculated as 75, and the study was conducted between February and August 2020 by using a content-validated questionnaire. Descriptive statistics had been utilized for data analysis, and Chi-square test had been applied for intergroup comparison (with \( P < 0.05 \) considered to be significant). Results: The mean age of the physicians who participated in this survey was 33.2 years. While 44% of them could identify all the potential advantages of using FDCs, only 09% could correctly recognize all the disadvantages associated with the same. Among the list of rational and irrational FDCs, only 49% could single out the irrational ones. And though the majority (83%) of the respondents do check for the rationality of FDCs before prescribing them, still out of 25 most commonly prescribed FDCs, 16 lacked any scientific justification for combination, and 09 (out of 16) had been banned by the Government of India. Conclusion: The outcome of this cross-sectional questionnaire-based study reflects the deficit in the knowledge regarding FDCs, as well as incoherence among the knowledge, attitude, and prescription practice. Though the physicians have cultivated a healthy attitude towards prescribing FDCs, the same is not reflected in their practice. In order to rectify these disparities, the authors have proposed certain recommendations within this article.

Keywords: Drug therapy, legislation, medical, pharmaceutical preparations, pharmacologic actions

Introduction

The objective of institutionalizing a safe and rational pharmacotherapy for the management of any disease or disorder is to provide either cure or palliation to the patients. And usually because of the nature of the disease and its debilitating effects, polypharmacy becomes inevitable. Owing to the burden associated with the same, such as increased pill count, reduced compliance to therapy, fixed-dose combinations (FDCs) were designed and introduced.\(^1\) Termed as “an innovative delivery mechanism,” the FDCs are a combination of one or more active ingredients to be used for a particular indication (s).\(^2\) But these combinations are considered to be rational if only they are able to fulfill certain criteria such as (to list a few) its pharmacokinetic property and quality is not inferior to the individual drugs, the efficacy gets enhanced as well as the incidence of the adverse effects reduces on combining the drugs, which in turn conduces better compliance, improved adherence, and simplified and cost-effective therapy.\(^3\)

There are a few diseases wherein these FDCs have proven to be beneficial over the single drug polypharmacy such as hypertension, tuberculosis, HIV infection, psychiatric disorders, and so on.

Apart from improving patient compliance, the other advantages offered by FDCs include improvement of the treatment
outcomes as well as reduced cost.\textsuperscript{[vi]} But the overlooked facet associated with them is the undesirable side effects, financial burden, and drug resistance, if not properly prescribed.\textsuperscript{[iv]} Yet the trend of their development and use is on the rise, especially through the previous decade, when one-third of the new drugs which were introduced in the market were FDCs.\textsuperscript{[vi, vii]} The major concern arises when some of these combinations are irrational, as they not only increase the financial burden over both the developers and users but can also produce significant adverse effects.\textsuperscript{[v]} In one of the recent analyses, it was found that out of 264 FDCs available in the market, only 54 were rational, whereas for the remaining, both the safety and effectiveness were a matter of question.\textsuperscript{[v]} Back in 2016, the Government of India (GOI) had banned around 344 FDCs, citing the reasons as the concern for users’ health or the lack of therapeutic justification; nonetheless, this decision was challenged in the court of law.\textsuperscript{[viii]} Again in September 2018, the GOI through a gazette notification banned 328 FDCs. Yet, the Current Index of Medical Specialties (CIMS), which is considered to be one of the major drug information resources, has listed more than 100 irrational and unapproved FDCs, which are still being marketed in India.\textsuperscript{[viii]} This cross-sectional survey-based study was undertaken with the prospect of not only identifying the lacunae in knowledge regarding FDCs but also to understand physicians’ attitude towards appreciating the rationality behind the combination of drugs, as well as their trend of prescribing the FDCs, and then recommending a few measures to correct any amiss. The current study was performed after approval from the Institutional Ethics Committee (letter no. 883/IEC-AIIMSRPR/2020 dated 10.02.2020).

**Methods**

This questionnaire-based survey was carried out from February 2020 to August 2020 among the physicians working at various designations (junior resident, senior resident, and faculty position) in All India institute of medical science (AIIMS) Raipur, Chhattisgarh, India. Initially, the study was planned to be conducted by contacting the physicians in-person, but due to unprecedented COVID-19 pandemic, the protocol was modified (dually approved by Institutional Ethics Committee), and the physicians were contacted by electronic means i.e. the questionnaire in the format of Google form was communicated either via e-mails or what’s app. The responses were recorded and saved electronically.

The sample size for the study was estimated using a standard formula for a finite population correction. As no similar study has been performed in the said population earlier, so considering the proportion of KAP for FDC to be 50%, with 95% confidence interval, 10% relative precision, and the total number of physicians working in the hospital to be 225, the sample size calculated was 68.\textsuperscript{[ix]} Based on this, the authors planned to interact and recruit at least 75 physicians (convenient sampling) belonging to different designations i.e. junior resident, senior resident, and faculty.

\[ n = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2(P)(1-P)} \]

Where \( n' \) = sample size with finite population correction, \( N \) = population size,

\( Z = \) statistic for a level of confidence \( (Z = 1.96) \), \( P = \) expected proportion \( (in \ proportion \ of \ one) \) \( (P = 50\%) \), and \( d = \) precision \( (d = 0.1) \)

Once the sample size was determined, the physicians posted in different departments at AIIMS Raipur were then communicated the questionnaire by electronic means. And a minimum of two reminders were also sent to them. Once the proposed sample size was achieved, the responses for the same were closed. The voluntary consent of participating physicians was equated to their willful submission of responses. And those who did not submit their responses were considered to be excluded.

The questionnaire was prepared by the authors after a thorough review of the literature available about FDCs. The contents of the questionnaire were assessed after consultation with the faculty of the same tertiary care hospital, who had a basic medical qualification and were holding a post-graduate degree in their respective fields. Each parameter in the questionnaire was reviewed and rated using a 4-point Likert scale \( (1 = \text{not relevant, 2 = somewhat relevant, 3 = relevant, 4 = very relevant}) \). The Content Validity Index (CVI) was then estimated, and accordingly parameters were validated.\textsuperscript{[x, xi]} The questions which were given a score of 3 or 4 by 80% of the faculty members were included in the questionnaire. This validated questionnaire which was then used for the survey consisted of four sections: A) Demographic details of the respondent, B) Knowledge of FDCs C) Attitude towards FDCs, D) Practice of FDCs. In the section A, participants were asked to provide information about their personal and professional backgrounds (age, sex, designation, qualification, and specialty). Section B was composed of seven statements to evaluate their knowledge of FDCs. The responses in this section were recorded as both dichotomous responses (yes/no) as well as multiple-choice responses. Also, a list of commonly used FDCs was provided in the questionnaire only, and the physicians were asked to identify whether they were rational or irrational. The next section, Section C, consisted of four statements to assess the attitude of the respondents towards prescribing FDCs. And the responses in this section were recorded as both dichotomous responses (yes/no) as well as multiple choices. The Section D also had four statements that were constructed to assess the practice of prescribing FDCs to the patients, and again the responses recorded in this section were dichotomous (yes/no).

As the study was carried out by contacting the physicians through electronic means, accordingly, it can be assumed that the bias which could have been encountered during this study is that the physicians who would be technologically sound, would be the ones who would have responded.
The data were presented using mean, standard deviation, and percentage. Furthermore, the intergroup comparisons were done by using the Chi-square test (wherein P value < 0.05 was considered statistically significant).

**Results**

A total of 221 invitations were sent out to fill in the questionnaire, but only 33.9% had responded to it, yet a predetermined sample size of 75 was achieved. Out of these 75 physicians who participated in the study, 27 were faculty members, 22 were senior residents, and 26 were junior residents. Their mean age was found to be 33.2 years (25–49 years), with 53 out of them being males [Table 1].

Almost all the physicians had reasonable knowledge about the FDCs and their definition. About half (56%) of the physicians considered that most of the marketed FDCs in India are irrational. And only 44% of them were aware of the FDCs which have been banned by the GOI. All the potential advantages and disadvantages that were listed in the questionnaire were identified correctly by 44% and 9.3% of physicians, respectively, indicating that physicians had a sound knowledge about the advantages associated with the use of FDCs as compared to disadvantages (P = < 0.00001). Regarding the identification of FDC as rational or irrational, out of 375 (5 * 75) responses, 86.1% (323/375) were correct in recognizing the rational ones out of the list. While only 184 out of 375 responses (49.1%) were correct in identifying the irrational FDCs. In comparison, a statistically significant difference was observed among the proportion of physicians who could correctly identify rational and irrational FDCs. The irrational FDCs were wrongly identified as rational by the majority. [Tables 2 and 3]

The majority of the physicians (96%) agreed that the prescription must be necessary to avail any FDC from the pharmacy.

| Table 1: Demographic and Professional Characteristics of Physicians |
|---------------------------------------------------------------|
| **Demographic Characteristics** |
| Age years (mean±SD) | 33.2±6.1 |
| Male:Female | 53:22 |
| Junior Residents | 26 |
| Senior Residents | 22 |
| Faculty Members | 27 |

| Table 2: Representation of Knowledge about FDCs among Physicians |
|---------------------------------------------------------------|
| **Criteria** | **Frequency (n)** | **Percentage** |
| Percentage of physicians who were aware about FDCs | 72/75 | 96 |
| Percentage of physicians who correctly identified definition of a FDC | 74/75 | 98.7 |
| Percentage of physicians who consider most of the FDCs marketed in India are irrational. | 42/75 | 56 |
| Percentage of physicians who were knowing about the FDCs banned by Government of India | 33/75 | 44 |
| Percentage of physicians who correctly identified all the potential advantages of FDCs | 33/75 | 44 |
| Percentage of physicians who correctly identified all the potential disadvantages of FDCs | 7/75 | 9.3 |
| Percentage of physicians who correctly identified rational FDCs as rational. | 323/375 | 86.1 |
| Percentage of physicians who correctly identified irrational FDCs as irrational. | 184/375 | 49.1 |

Round-about 52% of the physicians preferred to prescribe the same drugs as an FDC, rather than prescribing the drugs individually. About 51% of the physicians asserted that they update themselves about the statuses of FDCs every 12 months or more, followed by every 6-monthly (28%), 9 monthly (5.3%), and 3 monthly (16%). To check the rationality of an FDC, 24% of the physicians relied more on journals, followed by the CIMS (22.7%), continuous medical education (21.3%), essential medicines list (17.3%), textbooks (12%), and drug information by pharmaceutical companies (2.7%). [Table 4] About 83% of the physicians checked for the rationality of any FDC before prescribing it and prescribed FDCs by the generic name of the constituent drugs. A total of 53.3% of the physicians did educate the patients about the advantages and disadvantages of using an FDC. We could also collect around 25 different FDCs that were being prescribed in routine by the physicians, out of which, 16 appeared to be irrational or lacked any scientific justification for the combination, and 09 among them belonged to the list of the banned FDCs. Amoxycillin + clavulanic acid was the most commonly prescribed FDC in that list. [Table 5]

**Discussion**

This questionnaire-based KAP study was the first of its kind to be conducted at AIIMS Raipur, Chhattisgarh. With the overall response rate being 34%, the participation of female physicians in this study was found to be relatively lower, thus corroborating with the previous study.18 The mean age of the respondents was 33.2 years (25–49 years), thus indicating that the physicians who participated in this study were of a younger age group with considerably a longer professional period. And as young people are more adaptable and responsive towards changes required in attitude and practice as compared to the older ones, the recommendations of this study could thus be more useful for them.14

In the present study, no response was obtained from the physicians of >50 years of age. The possible explanations for the same may be inadequate technical expertise, unwillingness to fill an online form, reluctance to participate in the study, or an excessive workload. Akin to the previous studies, it was observed that almost all physicians were aware of the definition...
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And had the opinion that most of the FDCs being approved and marketed in India were irrational as seen recently with 328 FDCs getting banned by the GOI[8,17,18]. But the matter of concern arose when it was observed that around 56% of them were unaware of the commonly prescribed FDCs being banned by GOI.

For the questions which estimated the knowledge regarding advantages and disadvantages associated with the use of FDCs, with a list of the same being provided along, only 56% of the physicians could correctly identify the three common advantages, whereas 93% could not identify the disadvantages correctly from that list. Hence, the physicians were more aware of the advantages than the disadvantages associated with the use of FDCs. This echoes the habit of the physicians to unknowingly prescribe FDCs without looking out for the advantages or disadvantages it could offer. This observation could be linked with the habit of not prescribing FDCs mindfully.

Another evident observation in this study was about differentiating rational FDCs from irrational ones. A greater number of the physicians were not able to identify the irrational FDCs from the list (though the majority of them recognized rational ones), thus revealing that the respondents had relatively less knowledge regarding the irrationality of FDCs, which stands contradictory to their opinion that most of the FDCs marketed are irrational.

### Table 3: Comparison among Physicians for Parameters of Knowledge

| Criteria                                                                 | Chi-square value | P      |
|--------------------------------------------------------------------------|------------------|--------|
| Percentage of physicians who correctly identified all the potential advantages of FDCs vs Percentage of physicians who correctly identified all the potential disadvantages of FDCs | 23.04            | P<=0.00001 |
| Percentage of physicians who correctly identified rational FDCs as rational vs Percentage of physicians who correctly identified irrational FDCs as irrational. | 117.6            | P<=0.00001 |

### Table 4: Representation of Attitude and Practice about FDCs among Physicians

| Criteria                                                                 | Frequency (n) | Percentage |
|--------------------------------------------------------------------------|---------------|------------|
| Percentage of physicians who agreed prescription must be necessary to avail an FDC from the pharmacy | 72/75         | 96         |
| Percentage of physicians who preferred to prescribe same drugs as FDC over prescribing individually | 39/75         | 52         |
| Percentage of physicians who check for the rationally of an FDC before prescribing | 62/75         | 82.7       |
| Percentage of physicians who prescribe an FDC by generic name             | 62/75         | 82.7       |
| Percentage of physicians who educate patients about advantages and disadvantages of FDCs | 40/75         | 53.3       |

### Table 5: Most commonly prescribed FDCs

| Name                                                                 | Rational/Scientific Justification | Status in India* |
|---------------------------------------------------------------------|-----------------------------------|------------------|
| Amoxycillin + clavulanic acid                                       | Yes                               | Approved         |
| Ampicillin + Cloxacillin                                            | No                                | Approved         |
| Anti-tubercular drugs (Rifampicin + isoniazid + ethambutol + pyrazinamide) | Yes                               | Approved         |
| Ofloxacin + Ornizadole                                              | No                                | Banned           |
| Torsemide + spirinolactone                                          | Yes                               | Approved         |
| Telmisartan + hydrochlorhiazide                                     | Yes                               | Approved         |
| Glimepiride + Metformin                                             | No                                | Banned           |
| Estrogen + progesterone (OCP)                                       | Yes                               | Approved         |
| Levocetirzine + pheneylephrine                                     | No                                | Banned           |
| Levocetirzine + montelukast                                        | No                                | Banned           |
| Chlorpheneramine + pheneylephrine                                   | No                                | Banned           |
| Ambroxol + levosilbutamol                                           | No                                | Banned           |
| Paroxetine + clonazepam                                             | No                                | Banned           |
| Escitalopram + clonazepam                                           | No                                | Approved         |
| Risperidone + trifhexphenyndyl                                      | No                                | Approved         |
| Pregabalin + nortryptline                                           | No                                | Approved         |
| Levodopa + carbidoa                                                 | Yes                               | Approved         |
| Gabapentin + nortryptline                                           | No                                | Approved         |
| Lignocaine + adrenaline                                             | Yes                               | Approved         |
| Tamsulosin + dutasteride                                            | Yes                               | Approved         |
| Paracetamol + pheneylephrine                                        | No                                | Banned           |
| Diclofenac + serratistopetide                                        | No                                | Banned           |
| Pantoprazole + domperidone                                          | No                                | Approved         |
| Acclofenac + rabeprazole                                           | No                                | Banned           |
| Paracetamol + tramadol                                               | Yes                               | Approved         |

*Approved: Approved by Drug Controller General of India/state drug controller; Banned: Banned by Ministry of Health and Family Welfare, Government of India; OCP: Oral Contraceptive Pill
A larger proportion of physicians (96%) were in agreement with the fact that a prescription must be necessary for obtaining an FDC from the pharmacy, thus indicating their vigilant attitude (as schedule H and H1 drugs are not to be sold without prescription). And as the physicians were mindful of the advantages of the use of FDCs, this reflected in their choice (52%) of prescribing combinations over the individual drugs.

To check for the rationality of any FDC, most of the physicians resort to journals, considering it as an authentic source; however, it is quite uncommon to find the relevant articles on the same in reputed journals. In continuation, textbooks ranked last regarding the source of the rationality of FDCs, which was another revelation as the opinion was paradoxical to the fact that maximum information at a single point can only be found in textbooks, journals are here to supplement only. And as a greater proportion of physicians updated themselves regarding FDCs at an interval of 12 months or more, this could be attributed to why they were less observant about the banned FDCs which are widely published in the print and electronic media, and for which commentaries and reviews are also available.

A similar conflicting observation was found regarding the practice of prescribing FDCs. About 53% of physicians educated the patients regarding the advantages and disadvantages of FDCs, even though they themselves were partially aware of it (see results). Another critical finding in this regard is that among the most commonly prescribed FDCs, more than half (16/25) were found to be irrational/lacked any scientific justification, whereas nearly half had been banned by the GOI. While on one hand, this stance goes against their declaration of checking for the rationality of FDCs before prescribing, on the other hand, this disparity broadens up the major gap between the implementation of the ban and ongoing marketing of formulations, thus further illustrating pitfalls from both administrative and professional fronts. Apart from these undesirable conclusions, another commendable finding is that the physicians prefer to prescribe an FDC by the generic name of its constituents, rather than by its trade or brand name.

We will be focusing now on a few irrational yet approved FDCs we found in our list of commonly prescribed drugs.

Paroxetine + clonazepam and escitalopram + clonazepam, both FDCs are usually prescribed for managing major depressive disorder. Considering the expected adverse effects of anxiety/activity and insomnia, paroxetine and escitalopram are administered in the morning. Further, if insomnia is still significant, then clonazepam can be added at night, along with advising sleep hygiene and cognitive behavioral therapy. Using as an FDC, it would be difficult to administer either drug in the correct dose and timings. Furthermore, if patients report significant anxiety or insomnia (not getting relieved by SSRIs), then clonazepam can be added as an adjunct, even though studies prove that adding clonazepam does not provide sustained benefit, rather makes it difficult for the patient to cease the anxiolytics. The combination paroxetine + clonazepam itself belongs to category D as per notification by the GOI, and thus requires further data for its safe usage.

Gabapentin + nortryptiline and pregabalin + nortryptiline, both these FDCs are usually indicated in the management of peripheral neuropathy. But the drugs in these FDCs have got a variable dose range, require dose titration, especially in case if the patient has comorbid renal dysfunction. And as all three of them have a similar adverse effect profile, the additive effect cannot only severely deteriorate the quality of life but can also pose a threat to the life itself. More importantly, these combinations may prove to be disastrous in geriatric patients in whom renal functions are usually on a downfall. Lastly, these combinations also belong to category D.

The FDC of risperidone + trihexyphenidyl also lacks adequate scientific justification for combining the drugs of different groups. Risperidone is an atypical antipsychotic agent, indicated for the treatment of extrapyramidal toxicity arising with the use of antipsychotic agents. Being an anticholinergic, trihexyphenidyl may also have a negative effect on cognition, peripheral antimuscarinic effects, may exacerbate tardive dyskinesia, and cholinergic rebound following abrupt withdrawal along with the risk of abuse potential, hence making the combination irrational. In case of extrapyramidal side effects encountered, either the dose of the antipsychotic can be reduced or it can be switched with another anti-psychotics. Another combination, pantoprazole + domperidone has been in the market for a long, but a similar combination of rabeprazole + domperidone has been banned from marketing. The rationale behind combining a proton pump inhibitor with an antiemetic stands unjustified as peptic ulcer disease is not always associated with vomiting. And if proposed for gastro-esophageal reflux disease, then pro-kinetic drugs are not useful either alone or in combination with any acid suppressants.

The FDC of antibiotics like ampicillin + cloxacillin also lacks scientific justification as cloxacillin is primarily an antistaphylococcal agent, whereas ampicillin is effective against gram-negative organisms. The incidence of concurrent mixed infection is low; hence, the combination does not seem to have any added merit.

Based on the results of this study, which echoes clearly the substantial deficit in knowledge, attitude, and practice about FDCs, a few recommendations have been proposed by the authors. Improvising the teaching and training curriculum of the students inducted into the medical field could be a starting point as they would carry forward the same for their lifetime. This would not only improve their knowledge regarding FDCs but could also rectify their attitude and practice of prescribing drug combinations. As most FDCs lacking scientific justification
are prescribed at various levels of health care, for practicing physicians, information regarding the newly approved/banned FDCs as well as scientific rationality behind these combinations should be imparted by conducting frequent medical education programs. All these afore-mentioned interventions are targeted towards the professional front.

But for an FDC to stay in the market, the onus is shouldered not only by the physicians, but also by the administration that looks into the approval of the same, and the pharmaceutical companies which are responsible for manufacturing such FDCs. So, from the administrative point of view, a few recommendations that could help in eliminating the use of irrational FDCs could include making the approval process transparent with more detailed scrutiny of any FDC, increasing the manpower, as well as fixing the accountability of the approval committee/authority, and strictly supervising prohibition of the marketing of the banned FDCs. And also, the manufacturers must come forward with combinations having sound scientific rationale. The proposed FDCs should satisfy the criteria laid down by the Drugs Controller General of India (DCGI) i.e. the quality of the proposed drug combination should be similar to individual components, should offer advantages over individual prescriptions, pharmacokinetic properties must not be altered, and the combination must be free from disadvantages. 

The policies we make ultimately affect the common man who has to bear the consequences not only economically but also in terms of quality of life. Henceforth, certain interventions should also be directed towards introducing various approaches which help in increasing public awareness at least regarding the banned FDCs. The approach to limit the irrational FDCs from the Indian market is multisectorial. [Figure 1] The study has certain limitations as it gives an idea about the physicians of a single tertiary teaching hospital only. The responses were recorded by electronic means only. Parenteral preparations, nutraceuticals, and vitamin preparations were not discussed.

Conclusion

Through this cross-sectional study, the authors could figure out a few substantial deficits among physicians’ KAP for FDCs, which does necessitate urgent interventions. The rampant availability and prescription of irrational FDCs not only affects patients financially but also makes them vulnerable to adverse drug reactions. Furthermore, due to the use of irrational combinations, different drugs (especially antimicrobials) may over time lose their effectiveness. A few years back, 328 FDCs were banned, but the same was not implemented stringently. We require rapid action and rigorous implementation of policies that censor the use of FDCs not having a sound scientific basis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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