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ORIGINAL RESEARCH

Assessment of knowledge, attitude and practice of fixed-dose combinations amongst attending physicians and residents: a cross-sectional evaluation

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Abstract

Background: Fixed-dose combinations (FDCs) were brought into the market with the intent of providing benefits primarily to patients and physicians. Nevertheless, despite their multiple advantages, they have their own set of drawbacks, especially regarding irrational FDCs. If physicians continue to prescribe them, prohibiting their sale would become all the more challenging. This cross-sectional survey study was planned to comprehend the level of knowledge, attitude and practice of physicians regarding such FDCs at a tertiary care teaching institute of western Uttar Pradesh, India.

Methodology: A pre-validated questionnaire was communicated electronically to all the attending physicians. For data analysis, descriptive statistics were applied and a χ^2 test was performed for inter-group comparison.

Results: Amongst the 108 respondents, participation was almost comparable from both medical and surgical branches, with most participants being junior residents (58%). Even with sound knowledge of FDCs, only 46.30% of them were aware of banned FDCs. Similarly, only 6.48% could correctly identify the disadvantages associated with the use of FDCs, and 33.18% could correctly recognize irrational FDCs. This finding was consistently reflected in their attitude and practice and only 15.74% of respondents cross-referenced FDCs with the available literature. Furthermore, despite 88.89% of respondents checking for rationality of FDCs before prescribing them, a compendium of irrational FDCs is routinely prescribed.

Conclusion: To amend these shortcomings in prescribing of irrational FDCs, some recommendations are proposed by the authors herein.

Keywords: drug regulatory authorities, fixed-dose combinations, irrational combinations, pharmaceutical market.

Citation

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Introduction

Fixed-dose combinations (FDCs) are a combination of two or more active drug products in fixed ratio of doses into a single product.[1,2] When FDCs were introduced, the intent was to provide benefits for manufacturers and physicians as well as for afflicted patients. Patients often receive multiple drugs (polypharmacy) to address symptoms and/or cure a sundry of diseases with multimodal pathophysiological mechanisms as well as various infections, for example, cardiovascular diseases, diabetes mellitus, tuberculosis or human immunodeficiency virus infection.[3–5] Consequently, the increased pill burden, apart from affecting the patient's compliance towards therapy, additionally predisposes users to various drug–drug interactions, adverse drugs reactions (which could be misinterpreted as a new symptom thus resulting in supplementation of drugs) economic burden and reduced quality of life as well as increasing use of and burden on healthcare systems.[6,7]

FDCs were conceptualized and marketed to overcome the abovementioned issues[8] as well as to simplify therapy, improve pharmacokinetic and pharmacodynamic properties (improved bioavailability, synergistic action), enhance therapeutic effectiveness, reduce risk of resistance, and increase cost-effectiveness.[9–11] Yet,

some concerns related to their use warrant attention such as overpricing of combinations (compared with their single components), ascertaining offending drugs responsible for an adverse effect, clinical rationality of combinations, tailoring of treatment for different patients and potential for missing/consuming additional doses.[12] Furthermore, the ease of access and convenience of irrational FDCs may lead to their overconsumption.[12,13] Given these concerns, the Government of India banned 344 FDCs in 2016 and 328 FDCs in 2018. Yet, aside from these, more than 100 irrational combinations are still listed in the Current Index of Medical Specialities as well as being available in the market.[14,15] For a FDC to remain available in the market, the responsibility is shared by pharmaceutical companies, drug control departments and physicians who prescribe them. Therefore, we conducted a cross-sectional survey of physicians employed in our tertiary care teaching hospital to comprehend their level of knowledge regarding FDCs as well as their attitude towards analysing the rationality of and their practice of prescribing these FDCs. Knowledge, attitude and practice make up the triad of interactive factors, wherein knowledge reflects the level of understanding, attitude indicates preconceived ideas and feelings towards the concerned subject, and practice is a display of both knowledge and attitude.[16]

Methods

This cross-sectional descriptive study was conducted from July 2022 to September 2022 amongst the physicians (junior residents, senior residents and faculty members posted in clinical departments) appointed at Teerthanker Mahaveer Medical College & Research Centre (TMMC&RC), Moradabad, Uttar Pradesh, India. Data collection was initiated after receiving due approval from institutional ethics committee (vide letter number PH/No. 343/22 (Dept. of Pharmacology) dated 8 July 2022).

A pre-validated questionnaire was used for this purpose.[17] The questionnaire consisted of the following sections: (A) demographic details, (B) knowledge regarding FDCs, (C) attitude towards FDCs, and (D) practice of prescribing FDCs. To maintain anonymity, only the department and designation of the respondents were asked for in Section A. Section B was designed to assess the knowledge about FDCs; therefore, questions included in this section were not only limited to the identification of correct definition, advantages and disadvantages of use of FDCs but also questioned the correct identification of rational and irrational FDCs from the list provided. Section C pertained to respondents' attitude towards status of FDCs, and the responses collected under this section were both dichotomous and multiple choice. Finally, Section D encompassed questions related to practice of prescribing FDCs to the patients.

The sample size for this study was calculated by using finite population correction formula.[18]

$$n = NZ^2 P (1–P) / d^2 (N–1) + Z^2 (P) (1–P)$$

n=sample size; N=population size (388); Z=statistic for a level of confidence (1.96 for 95% confidence interval); P=expected proportion (50%); d=precision (0.05).

Considering the proportion of knowledge, attitude and practice regarding FDCs amongst the defined population to be 50% (as no such study had been conducted in the past in this institute), and with 95% confidence interval, 5% relative precision and 388 to be the overall number of physicians working in the TMMC&RC hospital, we determined the adequate sample size to be 180. Accordingly, to achieve this size, we sent the questionnaire to at least 200 physicians posted in various clinical departments and at different posts (junior residents, senior residents and faculty members).

For ease of participation of physicians (in view of their different outpatient department schedules), the questionnaire was sent electronically (via e-mail and personal messages), followed by two reminders. The wilful submission of their responses was considered equivalent to their voluntary consent for participation. The data collected were assessed and are presented as mean, standard deviation (SD) and percentages. For the intergroup comparison, we performed χ^2 test (with a *p* value of <0.05 as statistically significant).

Results

The authors reached out to 200 physicians working in the TMMC&RC hospital, with a response rate of ~54% (*n*=108). Out of these 108 participants, there was almost identical representation of physicians belonging to surgery and allied branches (53%, 57/108) and medicine and allied branches (47%, 51/108) (Figure 1A). Nevertheless, the majority of participants who replied to the survey were junior residents (58%, 63/108) followed by faculty members (26%, 28/108) and senior residents (16%, 17/108) (Figure 1B).

Knowledge

Most responders had a sound knowledge about what exactly FDCs are (i.e. they correctly identified the definition of FDC). However, less than half of them (46.30%, 50) were aware about the banned FDCs, and only 35.19% (38)

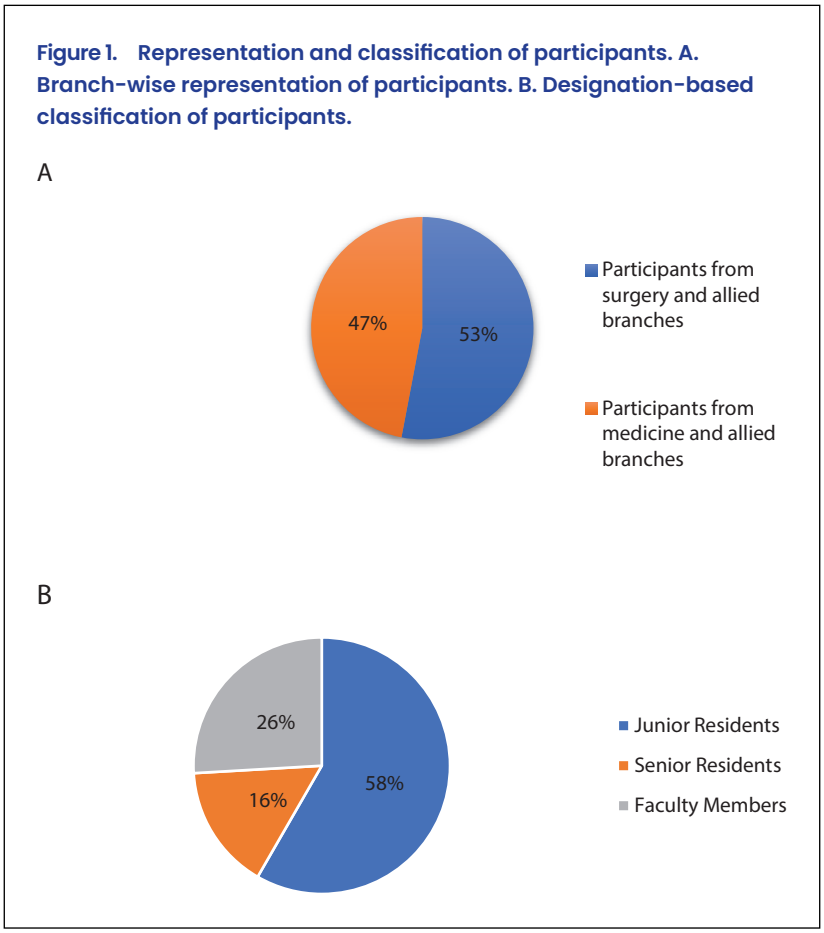


Figure 1. Representation and classification of participants. A. Branch-wise representation of participants. B. Designation-based classification of participants.

of the physicians considered that most of the FDCs marketed in India are irrational. When provided with a list of potential advantages and disadvantages associated with the use of FDCs, 39.82% (43) could correctly identify the advantages, whilst only 6.48% (7) could correctly identify the disadvantages, with the difference being statistically significant ($p<0.00001$). Similarly, a list of few commonly used both rational and irrational FDCs was provided in a questionnaire for identification, and out of 648 responses, 79.63% (516/648) had rightly identified rational FDCs whilst only 33.18% (215/648) identified irrational FDCs correctly, again reflecting a statistically significant difference ($p<0.00001$) (Table 1 and Figure 2).

Attitude

Answers to the questions aimed to assess prescriber attitudes towards FDCs in their clinical practice were quite interesting. The vast majority of participating physicians (95.37%, 103) felt that a prescription is required to obtain any FDC from a pharmacy. Additionally, more than half of participants (63.89%, 69) preferred to prescribe FDCs rather than individual drugs (Table 2). When enquired about the source they frequented to check for rationality of any FDC, the majority (34.26%, 37) relied on the Current Index of Medical Specialties and Monthly Index of Medical Specialties, followed by scientific medical journals (28.70%, 31), medical textbooks (15.74%, 17), Continuing Medical Education (12.04%, 13), Essential Medicines List (5.56%, 6) and information brochures provided by pharmaceutical companies (3.70%, 4) (Figure 3). Additionally, they were also asked about how frequently they updated

Table 1. Comparison of knowledge-related parameters amongst physicians.

Criteria	χ^2	*p* value
Proportion of physicians who correctly identified advantages associated with the use of FDCs *versus* proportion of physicians who correctly identified disadvantages associated with the use of FDCs	33.73	<0.00001
Proportion of physicians who correctly recognized rational FDCs as rational *versus* proportion of physicians who correctly recognized irrational FDCs as irrational	284.3	<0.00001

FDCs, fixed-dose combinations.

Figure 2. Illustration of knowledge-related parameters.

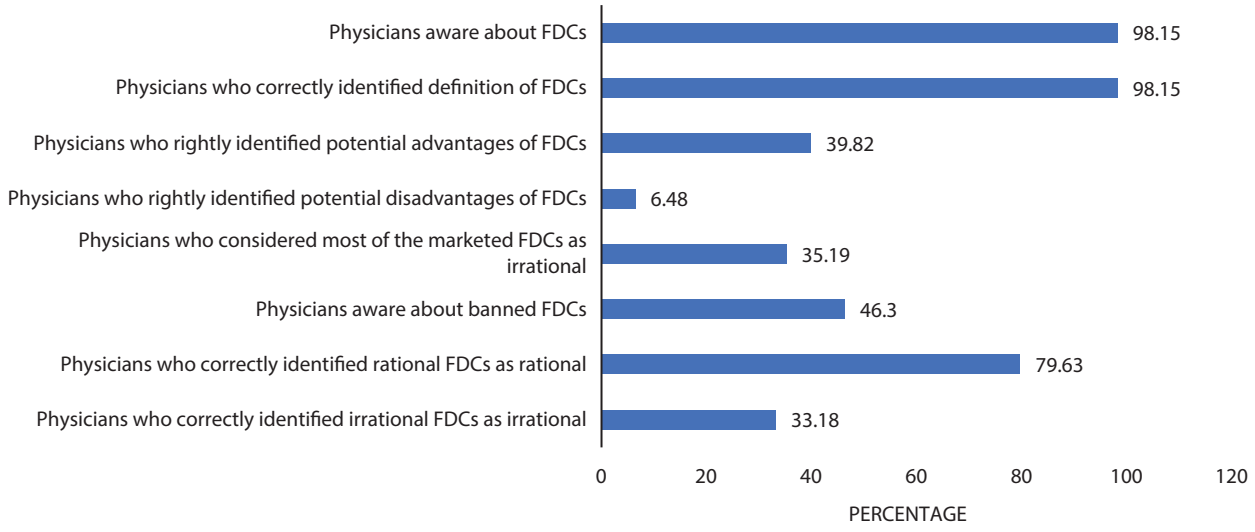


Table 2. Comparison of parameters related to attitude and practice.

Parameters	*n*	Percentage
Physicians who felt that prescriptions should be made necessary to avail FDCs	103/108	95.37
Physicians who prefer to prescribe FDCs rather than drugs individually	69/108	63.89
Physicians who check for rationality of FDCs before prescribing	96/108	88.89
Physicians who educate their patients about advantages and disadvantages of FDCs	83/108	76.85
Physicians who prescribe FDCs by generic name	67/108	62

FDCs, fixed-dose combinations.

themselves regarding FDCs marketed in India, and the majority asserted that they do so every 12 months (35.19%, 38), followed by every 6 months and 3 months (27.78%, 30 each), and every 9 months (9.26%, 10) (Figure 4).

Practice

Finally, physicians were asked about their routine practice of prescribing FDCs. On the one hand, 88.89% (96) of respondents stated that they check for rationality of FDCs before prescribing them whilst, on the other hand, only 62% (67) prescribed FDCs by generic name. Again, the majority (76.85%, 83) stated that they inform patients about the advantages and disadvantages associated with the use of FDCs (Table 2).

A list of approximately 30 different FDCs routinely prescribed by the physicians in their clinical practice was collected (Table 3), some of which were identified as being irrational or lacking scientific rationale as well as some have been banned by the Ministry of Health and Family Welfare.[19]

Discussion

The response rate of our survey-based study was almost half of the predetermined sample size (despite repeated reminders), yet we noticed almost equal representation from both the surgical and medical allied branches (53% and 47%, respectively). As observed in a study conducted in central India, we also found that, amongst the physicians who participated in our survey, the majority were junior residents whilst a lower proportion of faculty members responded to the survey; this could be due to digital proficiency of residents.[17]

In comparison to other studies,[13,20] the majority of the physicians who participated in our survey were generally aware of the concept of FDCs (98.15%), yet the worrisome observation was that a lesser proportion were aware of the banning of certain FDCs by the Government of India (46.30%). This was reflected in the low

Figure 3. Sources frequented to check rationality of fixed-dose combinations.

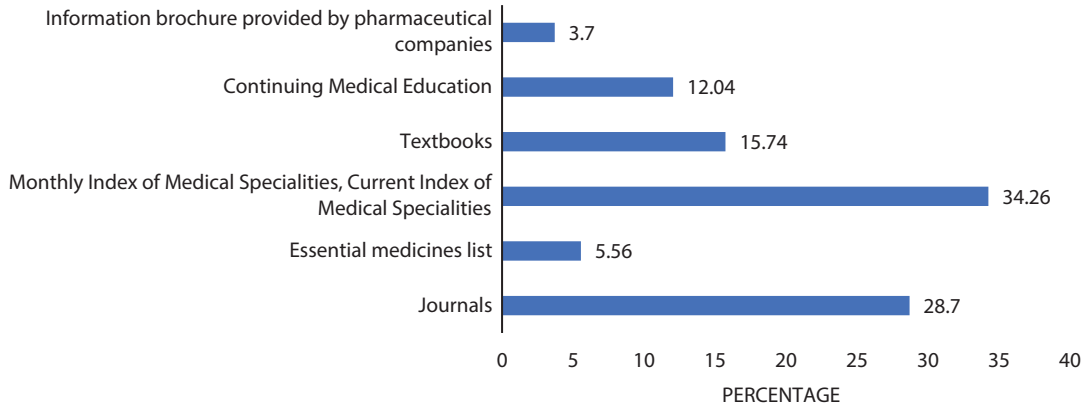
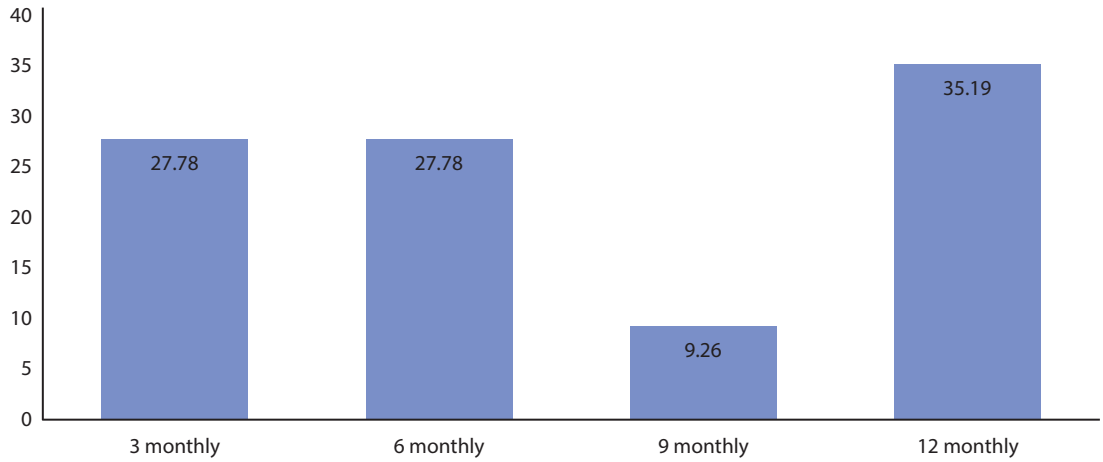


Figure 4. Frequency at which physicians update themselves about fixed-dose combinations.



proportion of physicians who consider that FDCs marketed in India are irrational (33.18%).

Unlike other cross-sectional studies that deliberated upon the advantages and disadvantages mentioned by the physicians,[20–22] we provided a list of the same in our questionnaire. Surprisingly, despite participating physicians having adequate knowledge about FDCs, more than 90% of them were unfamiliar with the disadvantages associated with their use. Likewise, more than 65% of respondents could not identify all the irrational FDCs that had been enumerated in the list of commonly used FDCs in clinical practice, akin to previous studies.[20–22] This somehow could be suggestive of their habit of prescribing FDCs offhandedly.

Appreciably, even though a smaller percentage of physicians felt that FDCs marketed in India are irrational, most (>95%) accepted that a valid recent prescription should be issued for their purchasing from any pharmacy, which is indicative of their vigilant attitude towards improper or rampant use of over-the-counter drugs. As in previous studies,[21,23] we also observed that physicians preferred to prescribe combination rather than individual drugs, thus echoing their awareness of the advantages associated with use of FDCs.

Physicians were further asked about the type of literature they would reference to check for rationality of FDCs and how frequently they update themselves regarding marketed FDCs. Ironically, physicians prefer to resort to the Current Index of Medical Specialties and the Monthly Index of Medical Specialties rather than reviewing textbooks or scientific medical journals, where the most up-to-date authentic information can be obtained. This was very much analogous to the observations made in

Table 3. List of routinely prescribed fixed-dose combinations.

Central nervous system	Cardiovascular system	Respiratory	Endocrinal	Antimicrobial	Gastrointestinal	Analgesics	Others
Levodopa + carbidopa	Telmisartan + amlodipine	Chlorpheniramine + paracetamol + phenylephrine	Glimepiride + metformin[a]	Amoxycillin + clavulanic acid	Pantoprazole + domperidone[a]	Diclofenac + paracetamol[a,b]	Mometasone + fusidic acid
	Aspirin + atorvastatin	Doxofylline + ambroxol		Cefuroxime + clavulanic acid[a]	Rabeprazole + domperidone[a]	Ibuprofen + paracetamol[a]	Moxifloxacin + dexamethasone
	Torsemide + spironolactone	Montelukast + levocetirizine		Antitubercular drugs		Paracetamol + aceclofenac + serratiopeptidase[a]	Tobramycin + fluorometholone
	Metoprolol + ramipril	Montelukast + fexofenadine		Ampicillin + clavulanic acid		Diclofenac + chlorzoxazone[a]	Moxifloxacin + ketorolac
	Furosemide + spironolactone			Ornidazole + ofloxacin[a,c]			Naproxen + domperidone
				Norfloxacin + tinidazole[a]			
				Piperacillin + tazobactam			
				Cefixime + sulbactam[a]			

[a]Irrational combinations (justification explained in the main text). [b]Injection of this combination is banned.[18] [c]Suspension and injection of this combination is banned.[18]

other studies, except for Sharma et al., who stated that residents preferred the use of textbooks.[13,16,20,21] Additionally, as the majority of participants would update themselves about banned FDCs at an interval of 12 months or more, this could be suggestive of their inattention towards gazette notifications issued by the Government of India.

Contrary to the above results, yet commendable, it that the vast majority of physicians stated that they check whether the combination they prescribe is rational or not and also inform their patients about the potential advantages of using FDCs. This is similar to the findings of Patil et al., who reported that ~95% of physicians participating in their survey speculated on the rationality of FDCs before prescribing them and 75% informed their patients about FDCs.[23] A pivotal finding observed from this survey was that, amongst the list of routinely prescribed FDCs, some were banned or irrational.[18] This observation is not only inconsistent with the respondents' assertion (checking rationality of FDCs before prescribing) but may augment the adversity of banning of irrational FDCs and their ongoing marketing in the Indian subcontinent.[16] Box 1 highlights some of the irrational FDCs collated from the survey and delineates what makes them irrational.[10,24–27]

Recommendations

Surmising on the data observed and evaluated, evidently indicative of a deficit of relevant and appropriate knowledge about FDCs as well as inconsonant attitude and practice skills, the authors would propose certain recommendations. Because the liability of irrational FDC prescription in the Indian pharmaceutical market is not only borne by practicing physicians, a multi-pronged concept needs to be outlined and implemented. This should involve the practicing and training physicians, regulatory authorities, pharmaceutical companies and consumers.[10] Pharmaceutical companies and industries should be cognizant about the compliance of FDCs produced with the rules prescribed by national regulatory authorities (Drug Controller General of India, DCGI) but also be wary of the national list of essential medicines, and they should generate robust data on pharmacokinetic, pharmacodynamic, efficacy and safety profile of these combinations. The regulatory authorities also need to be stringent and vigilant with the drugs being used in FDCs as well as the data being presented to them for marketing approval, apart from regularly reviewing the FDCs in market and taking decisive action accordingly. For the emerging physicians, improvising their teaching and training curriculum (comprehension of rationale behind FDCs as well as respective advantages and disadvantages offered by them) as well as teaching them about good prescribing practices could be worthwhile in dismantling the cascade commonly observed amongst departmental physicians of prescribing the same FDCs routinely. Similarly, practicing physicians should not just rely on the marketing representatives for data on FDCs

Box 1. Examples of irrational FDCs.

- Glimepiride and metformin combination is prescribed to manage diabetes mellitus. The administration of these drugs differs with respect to meals: glimepiride is to be consumed before a meal whilst metformin is to be taken after a meal. Using the combination would pose difficulty in the correct timing of administration.
- Combination of antimicrobials cefuroxime and cefixime with beta-lactamase inhibitors, such as clavulanic acid and sulbactam, is irrational, as these beta-lactamase inhibitors are not effective against the enzyme produced by gram negative bacilli.
- Combination of antiprotozoals and antibacterials, such as ornidazole and ofloxacin or tinidazole and norfloxacin, is irrational as dysentery or diarrhoea due to mixed infection (simultaneous amoebic and bacillary) rarely occurs; thus, either of the drug is being consumed unnecessarily, and this may also result in unexpected increased cost of treatment as well as high incidence of associated adverse effects.
- Proton pump inhibitors with antiemetics, such as pantoprazole or rabeprazole, with domperidone combinations are also irrational as their pharmacokinetic properties are not compatible and the timing of administration as well as dosing may not be concordant.
- Diclofenac or ibuprofen with paracetamol is a combination of analgesic and anti-inflammatory drugs, all of which act through same pathway and on same enzyme, yet do not have any synergism or added advantage over the stand-alone drugs. Additionally, their pharmacokinetic properties do not correlate, thus exposing patients to unwanted effects.
- Combinations of enzymes (serratiopeptidase) or skeletal muscle relaxants (chlorzoxazone) with analgesics (paracetamol, aceclofenac and diclofenac) are irrational as not only the efficacy of such combinations is unproven but also there is no synergism amongst them, merely adding to the cost of therapy and adverse events.

but should rather refer to a standard textbook frequently and attend regular continued medical education workshops. Consumers and patients should be informed to not rampantly purchase over-the-counter drugs or to prevent self-medication, and encouraged to visit a medical consultant and acquire a valid prescription. Governmental policies on public awareness regarding both the disadvantages and advantages associated with the use of FDCs, setting up of technical committees for reporting on FDCs or issues related to their use, updating laboratory standards, enhancing post-market surveillance as well as strengthening pharmacovigilance may be effective in general.[28–30]

Limitations

The calculated sample size could not be achieved despite repeated reminders sent out to the attending physicians and residents for participation in the survey. Additionally, all the responses were recorded by electronic means only. Finally, the perception shared and assessed in this study is of physicians employed in a single teaching tertiary care centre, which could limit the generalizability of the results.

Conclusion

Having a leverage in the Indian pharmaceutical market, FDCs were rolled out to provide advantages mainly to patients and physicians. Broadly, the advantages of FDCs include the simplification of therapy, better patient compliance and cost-effectiveness. Yet, with their use, disadvantages were also identified, including the mistaken justification for their combination, difficulty in tailoring individualized treatments and hindering the identification of offending drugs causing adverse effects. Considering the involvement of various stakeholders in the approval and marketing of FDCs, the present paper focused on assessing the knowledge, attitude and practice of physicians attending outpatient departments in one tertiary care centre. Astoundingly, the respondents who participated in our survey had deficits in appropriate knowledge, attitude and practice regarding FDCs as was evident by the low proportion of respondents aware that some marketed FDCs are irrational (35.19%) or have been banned by the Government of India under gazette notification (46.30%). Additionally, more than 90% of participants were unaware of the disadvantages of the use of some FDCs and more than 65% could not correctly identify irrational FDCs. Furthermore, only 27.78% of participants stated that they update themselves every 3 or 6 months about the current status of FDCs marketed in India and only 15.74% consulted textbooks to check the rationality of FDCs. This was substantiated by the list of routinely used FDCs collated, which did include banned or irrational FDCs. Consequently, the recommendations proposed herein may help reform and ameliorate the current scenario on marketing and use of FDCs, especially of irrational FDCs.

Contributions: DG and PSM were involved in conceptualizing and designing the study. DG, MT, PA, PS, SP and PSM were involved in acquisition, analysis and interpretation of data as well as drafting of manuscript. MT, PA, PS, SP and PSM critically reviewed the manuscript for all intellectual content. And all the authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article.

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