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Original Research

Availability and rationality of fixed dose combinations available in Kaduna, Nigeria

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Abstract

Background: Fixed-dose drug combinations (FDCs), are combinations of two or more active drugs in a single dosage form. Despite the advantages obtained from the use of these agents, there is increasing evidence questioning the rationality of several FDCs found in pharmaceutical markets-especially those in developing countries like Nigeria.

Objectives: To describe the availability of FDCs in drug retailing outlets located in Kaduna Nigeria, and to assess FDC registration status and inclusion on national and international essential medicines lists (EMLs). Rationality of selected FDCs was also assessed.

Methods: A cross-sectional survey was carried out from June to September 2018 in 60 registered pharmacies and patent medicine shops selected through multi-stage sampling. A data collection form was used to obtain information on the generic names and strengths of the active ingredients of the FDCs, their country of manufacture and evidence of registration with the Nigerian drug regulatory agency. To assess rationality, a scoring rubric developed from earlier studies was used. Data collected was coded and entered into a Microsoft excel 2016 spreadsheet for analysis. Descriptive statistics (frequencies and percentages) were used to report the data collected.

Results: FDCs encountered included 74 oral tablets/capsules, 52 oral liquids and 23 topical semi solids. Majority of the available FDCs were registered by Nigerian drug regulatory agency (91.5%), although only 8.5% and 6.5% in total were included on the Nigerian EML and the WHO model list respectively. Of the 99 FDCs assessed for rationality, 58 (58.6%) were found to be rational. Irrational FDCs included drugs acting on the respiratory tract (29.3%), analgesics (26.8%) and anti-infectives (22%).

Conclusions: A wide variety of FDCs were available in the study area, even though not all of them were rational. There is an urgent need for policy makers within the country to develop better detailed guidelines for FDC registration.

Keywords

Drug Combinations; Drug Therapy, Combination; Medication Adherence; Developing Countries; Nigeria

INTRODUCTION

Fixed-dose drug combinations (FDCs), are combinations of two or more active drugs in a single dosage form.¹ Several FDCs currently exist, but some of the more common combinations available include antibiotics, analgesics, antihypertensives, antidiabetics and drugs acting on the respiratory tract.²⁻⁴ The use of these drugs may offer several benefits to patients including reduced cost of treatment, and improved health outcomes from pharmacotherapy.⁵⁻⁷ Since many patients with chronic diseases like hypertension and diabetes will often require pharmacotherapy with multiple agents.⁶ For these patients, FDCs have the potential to simplify treatment regimens, increase adherence and improve patient outcomes.⁶⁻⁷ Furthermore-when used to treat infectious diseases, FDCs can increase the efficacy of drug treatment by broadening spectrum of activity.⁸

FDC use is also associated with several problems.^{1,8} Some of these disadvantages include difficulty with dosage alterations-as the dose of one drug cannot be altered without changing the dose of the other. Other potential

problems can be caused by the different pharmacokinetics of the constituent drugs, increasing the chances of unfavorable drug interactions & adverse drug effects. For antibiotic FDCs especially, the use of one or more broad spectrum antibiotics in combination can also cause serious problems for patients' e.g. antibiotic associated diarrhea and increased risk of developing resistance to one or more antibiotics.⁸

One of the major issues with FDCs is the issue of rationality.^{1,9} For an FDC to be considered rational, the drugs in the combination should act by different mechanisms and not have increased toxicity when combined. In addition, their pharmacokinetics must not be widely different.¹ Several studies from parts of Asia and Latin America have shown that many FDCs are not rational, and the government of some countries have banned several FDCs.^{2,4,9-11} FDC combinations so far been found to be problematic include several containing antibiotics, cough and cold medicines, antidepressants, Non-Steroidal Anti-inflammatory Drugs and antipsychotics.¹⁰⁻¹⁴

There is currently no published data on FDC availability and rationality in Nigeria. Therefore, this study was designed to describe the availability and assess the rationality of selected FDCs available in drug retailing outlets in Kaduna state, Nigeria. In addition, FDC inclusion on the 6th edition of the Nigerian essential medicines list and the 20th edition of the World Health Organization (WHO) model list of essential medicines were also assessed.^{15,16}

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METHODS

Ethical Considerations

Ethical approval was obtained from the human research ethics committee of Ahmadu Bello University; (Approval number: ABUCUHSR/2018/UG/008). No information that could be used to identify the visited premises was collected, and the study did not involve any patient contact.

Study Sites

The study was carried out in Kaduna state-the fourth largest state-by land mass- in Nigeria. The state has 23 local government areas and a population of over six million inhabitants-according to 2006 official census figures.¹⁷ The state contains three major urban areas: Kaduna metropolis, Kafanchan and Zaria.¹⁸ Because over 95% of all the registered pharmacies in the state are located within two of these areas-Kaduna metropolis and Zaria, this study was carried out in those areas.¹⁹

There are two types of retail drug outlets within Nigeria-community pharmacies and patent medicine stores. Community pharmacies are run by pharmacists, while patent medicine stores are operated by Patent and Proprietary Medicine Vendors (PPMVs). PPMVs are individuals without formal training in pharmacy who are allowed by law to sell pharmaceutical products/medicines.²⁰ They were initially established by the Nigerian government, to improve access to medicines in communities with limited access to essential health commodities. However they now co-exist with, and are suspected to even outnumber registered community pharmacies within the country.²⁰ This study was carried out in both types of outlets.

Study design and sampling method

A cross-sectional survey was carried out from June to September 2018 in selected pharmacies and patent medicine stores.

Multi-stage sampling was used to select pharmacies and patent medicine stores to be visited. Given the large size of Kaduna metropolis, it was divided into two major areas-Kaduna north and Kaduna south. These two areas plus Zaria town were then subdivided into ten major suburbs each, making a total of 30 suburbs. Registered pharmacy premises in the state were then classified based on their locations into one of these 30 suburbs. One pharmacy premise was then randomly sampled from each group-making a total of 30 pharmacies. There is currently no similar list of registered patent medicine shops in the state, so convenience sampling was also used to select one patent medicine store from each suburb-also making 30 patent medicine stores. All sampled pharmacies and patent medicine stores were eligible to participate if they were willing to allow the researcher access to their shops. If not, they were excluded and another pharmacy/ patent store randomly selected.

Data collection instrument

A form was designed to collect the data. The form collected data on: the dosage form of the FDC; Generic names and strengths of the active ingredients; country of manufacture and evidence of registration with the Nigerian drug regulatory agency –the National Agency for Food and Drug Administration and Control (NAFDAC).

Data collection

Shop owners or other personnel working in the visited premises were initially approached and informed about the objectives of the study. Afterwards, their permission was sought to collect data from their shops. If they agreed, the

Table 1. Scoring rubric used to assess rationality

| Item | How it was assessed | Scoring |
|---|--|---|
| Registration status of API(s) | NAFDAC Drug registration database was checked | Depending on the number of drugs in the FDCs. If two, score 0.5 each for each drug listed on the NAFDAC drug database, if three score 0.33 each, and so on. . Exclude drugs not used singly from this analysis |
| FDC listing in Nigerian or WHO Essential Medicines List | Manual check of both lists | If listed in only one Essential Medicines List (Nigerian /WHO model list), score half but if both, score 1 |
| Efficacy of API | Check of relevant drug monograph on Medscape or drugs.com | Depending on the number of drugs in the FDCs. If two, score 0.5 each for each drug as long as there is evidence of its efficacy. If three, score 0.33 each, and so on. Exclude drugs not used singly from this analysis |
| Efficacy of the FDC | Search of the online database- drugs.com | If there is a monograph for the FDC-score 1, otherwise score 0. |
| Pharmacokinetics | Check for interactions using the online Medscape drug interaction checker, | If favorable - score 1. If unfavorable, score -1 and if none, score 0. |
| Pharmacodynamics | Standard Pharmacology textbooks | If FDC components have similar mechanism of action, score 0 but if their mode of action is different, score 1 |
| Advantage of reduced dose | Relevant drug monograph on Medscape or drugs.com | Depending on the number of drugs in the FDCs. If two, score 0.5 for each API that is used at a lower dose than usual. If three, score each reduced dose API 0.33 and so on. |
| Advantage of convenience | | If the pill count/ dose of FDC is less than taking the individual components singly, score 1. If not, score zero |
| * Drug interactions were only checked for active ingredients. We defined favorable PK interactions as situations where one AI had beneficial effects on another by prolonging one of its PK parameters. API: Active Pharmaceutical Ingredient; FDC: Fixed Dose Combination; WHO: World Health Organization; NAFDAC: National Agency for Food and Drug Administration | | |

| Dosage form | No of FDCs available; n (%) | No. of APIs present | Average no of APIs |
|-----------------------|-----------------------------|---------------------|--------------------|
| Oral tablets/Capsules | 74(48.4) | 2-4 | 2.2 |
| Oral liquids | 52(34) | 2-6 | 3.1 |
| Topical semi-solids | 23(15) | 2-5 | 3 |
| Injectables | 2 (1.3) | 2 | 2 |
| Pessaries | 2 (1.3) | 2-3 | 2.5 |

researcher identified medication containing more than one active ingredient and collected relevant information from the drug packaging. Only drugs containing at least one known active pharmaceutical ingredient for which there was some evidence of efficacy were included in the study. On this basis, multivitamin, nutraceutical and herbal FDC formulations were excluded. In addition, data was also not collected for other categories of FDCs including parenteral fluids and inhalers/aerosols. Data was only collected once for each FDC combination, so even if the same combination was produced/marketed by a different pharmaceutical company, data was not collected again.

Data analysis

Data collected was coded and entered into a Microsoft excel spreadsheet for analysis. Descriptive statistics (frequencies and percentages) were used to report the data collected.

To check if a particular FDC was present on the Nigerian essential medicines list (6th Ed, 2016) or the World Health Organization (WHO) model list of essential medicines (20th Ed, 2017), a manual search of both lists was carried out.

To assess rationality, a scoring rubric was developed from checklists used in earlier studies by Dalal *et al.* and Shah *et al.*^{4,11} After modification, the final checklist contained eight items, each of which could be scored a maximum of one mark-making eight the highest achievable score by any FDC. See Table 1 for further details of the scoring rubric. Things assessed by this rubric included: the NAFDAC registration status of each Active Pharmaceutical Ingredient (API) in the FDC and whether the pharmacodynamics and pharmacokinetics of the active ingredients in the FDC were favorable. We also assessed whether there was any evidence for the efficacy of the FDC, which we defined as the presence of a monograph on the FDC on either drugs.com or Medscape stating that the FDC could be used to treat/manage one or more conditions.

To decide on a cutoff value for rationality, seven FDCs included on both the Nigerian and the WHO model Essential Medicines Lists (EMLs) were assessed using the scoring rubric, and their average score (5) chosen as the cutoff.

RESULTS

A variety of FDCs (n=153) in different forms were available

at the visited outlets. The number of active pharmaceutical ingredients in these FDCs ranged from two to six (Table 2). Majority of the FDCs were manufactured in Nigeria (36.6%) and India (33.6%), while the others were produced in other countries including the United Kingdom, France, Egypt and others

Available FDCs could be classified into several pharmacological classes. The analgesics contained at least one Non-steroidal anti-inflammatory drug (NSAID), while anti-infectives were mostly antibiotic combinations, and a few anti-malarial drugs.

Majority of the oral solid fixed-dose combinations were antihypertensives and anti-infectives (Table 3). Similarly, over half of the oral liquid FDCs were drugs acting on the respiratory tract-especially cold and cough preparations. Most of the topical semi-solid FDCs encountered were anti-infective drugs containing antibiotic, antifungal and corticosteroid combinations.

Majority of the available FDCs were registered by the Nigerian drug regulatory agency. However, less than 10% of them in total were found to be included on either the Nigerian essential medicines list or the WHO model list of essential medicines (Table 4).

Rationality was assessed for all of the oral tablets (n=74) and selected oral liquid FDCs (n=25) encountered. The other liquid FDCs that were not assessed either also came in oral tablet forms (i.e. they had already been evaluated), or they were FDCs acting on the gastrointestinal or respiratory tracts that contained more than two APIs that could not be used individually for treatment.

Using a cut-off mark of five out of the total score of eight, 62% (n=46) of the available oral solid FDCs and 48% (n=12) of oral liquids were found to be rational. Of the 41 FDCs found to be irrational, Drugs acting on the respiratory tract (n=12), analgesics (n=11) and anti-infectives (n=9) were the most implicated FDC drug classes.

DISCUSSION

The aim of this study was to describe the availability of fixed-dose combination products sold within the studied areas and to assess the rationality of selected FDCs. Study findings showed that there were a wide variety of FDCs available in the study areas. While majority of the FDCs

| Pharmacological Class | Oral tablets n (%) | Oral Liquids n (%) | Topical semi-solids n (%) | Injectables n (%) | Pessaries n (%) |
|--|--------------------|--------------------|---------------------------|-------------------|-----------------|
| Anti-hypertensives | 19 (25.7) | 0 | 0 | 0 | 0 |
| Anti-infectives | 18 (24.3) | 11 (21.2) | 14 (63.6) | 02 (100) | 02 (100) |
| Drugs acting on the respiratory tract | 06 (8.1) | 29 (55.8) | 0 | 0 | 0 |
| Anti-diabetics | 06 (8.1) | 0 | 0 | 0 | 0 |
| Others (Contraceptives and centrally acting drugs) | 05 (6.8) | 0 | 0 | 0 | 0 |
| Drugs acting on the gastrointestinal Tract | 04 (5.4) | 09 (17.3) | 0 | 0 | 0 |

| Table 4. FDC local registration status and Presence on National and International EMLs | | | | | |
|--|-----------------------|-----------------------|----------------------|----------------------|--------------------|
| Description | Oral tablets n (%) | Oral liquids n (%) | Semi solids n (%) | Injectables n (%) | Pessaries n (%) |
| Presence of NAFDAC Registration | 69(93.2%) | 46(88.5%) | 21(91.3%) | 2(100%) | 2(100%) |
| Presence on the National EML | 9(12.2%) | 3(5.8%) | 0(0%) | 1(50%) | 0(0%) |
| Presence on the WHO model list | 8(10.8%) | 1(1.9%) | 0(0%) | 1(50%) | 0(0%) |

were registered with the Nigerian drug regulatory agency, some of the combinations were found to be irrational.

Several studies have reported that FDCs are widely available in several countries including India and Nepal, as was the case in this study. Similarly, the most common pharmacological classes encountered, number of APIs and dosage forms of available FDCs in this study all followed similar trends to the results reported in these studies.^{3,4,11}

Most of the FDCs encountered during this study were registered by the Nigerian drug regulatory body, even though quite a few of them were found to be irrational. In contrast, studies from other parts of the world have reported fairly high numbers of unregistered FDCs within their pharmaceutical markets.^{10,13,14} Although FDC registration is important, this is however not as important as the need to develop definitive criteria to register these drugs. While regulatory authorities in developed countries have recognized the importance of FDCs, and developed specific guidelines for their registration and control, this is not the case in some developing countries.^{4,10,21} Results from this study also seem to suggest that Nigeria might be one of these countries.

Essential medicines are drugs rationally chosen to satisfy the health care needs of the majority of the population.²² These drugs are included on essential medicines lists, and have sufficient scientific data supporting their use. Less than 10% of the available FDCs in this study were included on either the Nigerian or WHO model essential medicine lists. This is very similar to results from other studies on this topic, that have all reported that only around 10% or less of the FDCs in their studies could be found on the EMLs of their specific countries or on the WHO model list.^{3,4,11}

Of the 99 drugs assessed for rationality in this study, over half of them were found to be rational. Majority of these rational FDCs were antihypertensives and antidiabetics. Several antihypertensive FDCs offer better blood pressure control and improved patient medication adherence when compared with free drug combinations.^{7,23} Furthermore, antihypertensive FDC use may also reduce the occurrence of adverse effects associated with treatment.²³ In the same vein, oral antidiabetic FDC use by patients is associated with lower health care costs, better patient compliance and a higher likelihood of HbA1c goal attainment.^{5,24}

Conversely, Majority of the irrational FDCs in this study were drugs acting on the respiratory tract, analgesics and

anti-infectives. Other studies that have assessed FDC rationality have also reported problems with several FDCs within those drug classes.^{4,11,12} Studies by Roy *et al.* and Shah *et al.* have all reported that substantial proportions of FDCs acting on the respiratory tract are not rational.¹² Similar problems have been reported with anti-infective FDCs, with several researchers questioning the pharmacological and therapeutic basis for several antibiotic containing FDCs.^{12,14} In addition, even though this study did not assess the rationality of encountered topical FDCs. Many of the most common type of topical FDCs in our study (FDCs containing antibiotics, antifungals and corticosteroids) have also been reported to be irrational, and several of them have been banned by the Indian government.^{25,26}

Limitations of this study include the nature of the sampling technique used. While we tried to cover as wide an area as possible, we cannot be sure that we didn't inadvertently miss some available FDCs. In addition, this study was carried out in only one state within the country, and may not be fully generalizable to others. Finally, we can also not totally rule out the possibility that our scoring rubric and selected cut off score of five might have over or underestimated actual FDC rationality.

CONCLUSIONS

In conclusion, a wide variety of FDCs were available and most of them were found to be registered by the Nigerian drug regulatory agency. Only a few of the available FDCs were included in the essential medicine lists of Nigeria and that of the WHO, and several FDCs were found to be irrational. Findings from this study suggest that there is an urgent need for policy makers and drug regulatory authorities within the country to develop better detailed guidelines governing the registration of FDCs, and ensure that FDCs are only registered if there is sufficient data supporting their effectiveness and safety.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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References

- Gautam CS, Saha L. Fixed dose drug combinations (FDCs): rational or irrational: a view point. Br J Clin Pharmacol. 2008;65(5):795-796. <https://doi.org/10.1111/j.1365-2125.2007.03089.x>
- Wirtz VJ, Mol PG, Verdijk J, Vander Stichele RH, Taxis K. Use of antibacterial fixed-dose combinations in the private sector in eight Latin American Countries between 1999 and 2009. Trop Med Int Health. 2013;18(4):416-425. <https://doi.org/10.1111/tmi.12068>
- Poudel A, Mohamed Ibrahim MI, Mishra P, Palaian S. Evaluation of the registration status of fixed-dose drug combinations in Nepal. J Pharm Health Serv Res. 2018;9(1):41-46. <https://doi.org/10.1111/jphs.12205>

4. Dalal K, Ganguly B, Gor A. Assessment of rationality of fixed dose combinations approved in CDSCO List. *J Clin Diagn Res.* 2016;10(4):FC05-FC08. <https://doi.org/10.7860/JCDR/2016/17856.7691>
5. Lokhandwala T, Smith N, Sternhufvud C, Sörstadius E, Lee WC, Mukherjee J. A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination vs loose-dose combination of oral anti-diabetes drugs. *J Med Econ.* 2016;19(3):203-212. <https://doi.org/10.3111/13696998.2015.1109518>
6. Harris SB. The power of two: an update on fixed-dose combinations for type 2 diabetes. *Expert Rev Clin Pharmacol.* 2016;9(11):1453-1462. <https://doi.org/10.1080/17512433.2016.1221758>
7. Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: A population-based retrospective cohort study. *PLoS Med.* 2018;15(6):e1002584. <https://doi.org/10.1371/journal.pmed.1002584>
8. ReAct. Why are fixed dose combinations of antibiotics generally not a good idea?. <https://www.reactgroup.org/news-and-views/news-and-opinions/year-2018/why-are-fixed-dose-combinations-of-antibiotics-generally-not-a-good-idea/> (accessed Dec 28, 2018).
9. Ahmad A, Khan MU, Balkrishnan R. Fixed-dose combination antibiotics in India: global perspectives, *Lancet Glob Health.* 2016;4(8):e521. [https://doi.org/10.1016/S2214-109X\(16\)30093-6](https://doi.org/10.1016/S2214-109X(16)30093-6)
10. Poudel A, Mohamed Ibrahim MI, Mishra P, Palaian S. Assessment of the availability and rationality of unregistered fixed dose drug combinations in Nepal: a multicenter cross-sectional study. *Glob Health Res Policy.* 2017;2:14. <https://doi.org/10.1186/s41256-017-0033-z>
11. Shah S, Patel J, Desai M, Dikshit RK. Critical analysis of antimicrobial and respiratory fixed dose combinations available in Indian market. *Int J Med Public Health.* 2015;5(2):161-164. <http://dx.doi.org/10.4103/2230-8598.153828>
12. Roy V, Malhotra R, Tayal V, Bansal A, Gupta KS. Fixed-dose combinations for cough and common cold in India: an assessment of availability and rationality. *Fundam Clin Pharmacol.* 2011;25(2):258-266. <https://doi.org/10.1111/j.1472-8206.2010.00840.x>
13. McGettigan P, Roderick P, Mahajan R, Kadam A, Pollock AM. Use of Fixed Dose Combination (FDC) Drugs in India: Central Regulatory Approval and Sales of FDCs Containing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Metformin, or Psychotropic Drugs. *PLoS Med.* 2015;12(5):e1001826. <https://doi.org/10.1371/journal.pmed.1001826>
14. McGettigan P, Roderick P, Kadam A, Pollock A. Threats to global antimicrobial resistance control: Centrally approved and unapproved antibiotic formulations sold in India. *Br J Clin Pharmacol.* 2019;85(1):59-70. <https://doi.org/10.1111/bcp.13503>
15. FMOH, Essential Medicines List Nigeria 6th Edition, Federal Ministry of Health Nigeria, Abuja, 2016.
16. WHO, WHO Model List of Essential Medicines-20th List, World Health Organization, 2017.
17. NPC, Population Distribution by Sex, State, LGA & Senatorial District, National Population Commission, Nigeria, Abuja, 2010.
18. KDSG, Demographics – Kaduna State Government, 2018. <https://kds.gov.ng/demographics/> (accessed Dec 28, 2018).
19. PCN, List of Licensed Pharmacists and Licensed Pharmaceutical Premises, Pharmacists Council of Nigeria, Abuja, 2016.
20. Beyeler N, Liu J, Sieverding M. Systematic review of the role proprietary and patent medicine vendors in healthcare Provision in Nigeria. *PLoS One.* 2015;10(1):e0117165. <https://doi.org/10.1371/journal.pone.0117165>
21. Desai D, Wang J, Wen H, Li X, Timmins P. Formulation design, challenges, and development considerations for fixed dose combination (FDC) of oral solid dosage forms. *Pharm Dev Technol.* 2013;18(6):1265-1276. <https://doi.org/10.3109/10837450.2012.660699>
22. Hogerzeil HV. The concept of essential medicines: lessons for rich countries. *BMJ.* 2004;329(7475):1169-1172. <https://doi.org/10.1136/bmj.329.7475.1169>
23. Gupta AK, Arshad S, Poulter NR. Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents. *Hypertension.* 2010 Feb;55(2):399-407. <https://doi.org/10.1161/HYPERTENSIONAHA.109.139816>
24. Williams SA, Buysman EK, Hulbert EM, Bergeson JG, Zhang B, Graham J. Hemoglobin A1c outcomes and health care resource use in type 2 diabetes mellitus patients treated with combination oral antidiabetic drugs through step therapy and loose-dose and fixed-dose combinations. *Manag Care.* 2012;21(7):40-48.
25. Kumar S, Goyal A, Gupta YK. Abuse of topical corticosteroids in India: Concerns and the way forward. *J Pharmacol Pharmacother.* 2016;7(1):1-5. <https://doi.org/10.4103/0976-500X.179364>
26. Pande S. Steroid containing fixed drug combinations banned by government of India: A big step towards dermatologic drug safety. *Indian J Drugs Dermatol.* 2016;2(1):1-2. <https://doi.org/10.4103/2455-3972.184102>